Original Article / Özgün Araştırma

Effective Loading Dose of Dexmedetomidine to Induce Adequate Sedation in Parturients Undergoing Caesarean Section Under Spinal Anaesthesia

Spinal Anestezi Altında Sezaryen Doğum Ameliyatı Olan Gebelerde Yeterli Sedasyonu Başlatmak İçin Etkin Deksmedetomidin Yükleme Dozu

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Abstract / Öz

Objective: To calculate the effective dose (ED) of dexmedetomidine for caesarean section under spinal anaesthesia.

Methods: Consecutive parturients scheduled for caesarean section under spinal anaesthesia were included. The loading dose of dexmedetomidine was evaluated using the up-and-down method, starting at 1.0 μg kg^{-1} and a step size of 0.1 μg kg^{-1}. The loading dexmedetomidine was administrated by the venous route for 10 min, and afterwards a maintenance dose began at a rate of 0.3 μg kg^{-1} h^{-1} in all parturients. Adequate sedation was defined as a Ramsay sedation score ≥3. The ED50 and ED95 of loading dexmedetomidine were calculated using probit regression.

Results: The ED50 and ED95 of loading dexmedetomidine for adequate sedation were 0.82 μg kg^{-1} (95% confidence intervals [CI] 0.73–0.89 μg kg^{-1}) and 0.96 μg kg^{-1} (95% CI 0.90–1.39 μg kg^{-1}), respectively.

Conclusion: The ED50 and ED95 of loading dexmedetomidine to achieve adequate sedation were 0.82 μg kg^{-1} and 0.96 μg kg^{-1} for caesarean section under spinal anaesthesia.

Keywords: Dexmedetomidine, sedation, spinal anaesthesia, effective dose

Amaç: Çalışmanın amacı, anestezi altında yapılan sezaryen ameliyatında etkin deksmedetomidin dozunu hesaplamaktır.

Yöntemler: Spinal anestezi altında sezaryen doğum planlanan ardışık gebeler çalışmaya dahil edildi. Yukarı-aşağı (up-down) yöntemi kullanılarak ve 1,0 μg kg^{-1} dozla başlayıp 0,1 μg kg^{-1} doz değerinde değişiklikler yaparak deksmedetomidin yükleme dozu değerlendirildi. Tüm gebelerde, deksmedetomidin yükleme dozu 10 dakika boyunca venöz yolla uygulandı ve daha sonra idame dozuna 0,3 μg kg^{-1} s^{-1} oranında başlanıldı. Ramsay sedasyon skoru ≥3, yeterli sedasyon değeri olarak tanımlandı. ED50 ve ED95 deksmedetomidin yükleme dozu probit regresyon analizi kullanılarak hesaplandı.

Bulgular: Yeterli sedasyon için ED50 ve ED95 deksmedetomidin yükleme dozu sırasıyla 0,82 μg kg^{-1} (%95 güven aralığı (GA) 0,73-0,89 μg kg^{-1}) ve 0,96 μg kg^{-1} (%95 GA 0,90-1,39 μg kg^{-1}) olarak bulundu.

Sonuç: Spinal anestezi altında yapılan sezaryen doğum ameliyatında yeterli sedasyona ulaşmak için ED50 ve ED95 deksmedetomidin yükleme dozları 0,82 μg kg^{-1} ve 0,96 μg kg^{-1} olarak değerlendirildi.

Anahtar Sözcükler: Deksmedetomidin, sedasyon, spinal anestezi, etkin doz

Introduction

Although spinal anaesthesia has the advantage of reduced neonatal exposure to potentially depressant drugs, parturients who are awake during surgery may suffer anxiety, fear and stress, and spinal anaesthesia is associated with a high incidence of maternal hypotension (1). Dexmedetomidine is widely used as a sedative because of its minimal respiratory depression and being easy to wake up from (2, 3). Hypotension and bradycardia, which are major side effects of dexmedetomidine, occur in a dose-related manner (3-8), and spinal anaesthesia can produce significant sedation (9, 10). Therefore, spinal anaesthesia might alter the dose needed for loading and maintenance, so it should be titrated according to the individual patient's need if a certain level of sedation is targeted. We found no reports in the literature about the use of dexmedetomidine among pregnant patients. The purpose of this study was to calculate the effective dose (ED) of loading dexmedetomidine for caesarean section under spinal anaesthesia.

Methods

Ethics approval was obtained from the Ethics Board of our hospital. Consecutive parturients who were to undergo caesarean section were asked for written informed consent and enrolled in the study. Parturients with contraindications to combined spi-

nal epidural anaesthesia, liver insufficiency, kidney insufficiency, or neurological illness were removed from this clinical trial.

When the parturients arrived at the operating room without any premedication, oxygen was applied via a nasal cannula at 3 L min⁻¹. Before spinal anaesthesia, the parturients received 5 mL kg⁻¹ Ringer's lactated solution over 20 min. Combined spinal epidural anaesthesia was performed at the L2-3 intervertebral space in the left side-lying position using a combined spinal epidural set (Henan Tuoren Medical Equipment Group Co. Ltd, Changyuan, China). A 16-gauge epidural needle was used for epidural puncture, and a 25-gauge spinal needle was used for spinal injection through the inside of the epidural needle. After successful spinal puncture, the mixed solution containing 1 mL or 1.1 mL (1 mL for patients <165 cm in height and 1.1 mL for patients ≥165 cm in height), 0.75% bupivacaine (Shanghai Zhaohui Pharmaceutical Co. Ltd, Shanghai, China), 25 μg (0.5 mL) fentanyl (Yichang Humanwell Pharmaceutical Co. Ltd, Yichang, China) and 0.5 mL 10% glucose was injected for spinal anaesthesia. A catheter was indwelled in the epidural space, and the patient was returned to a supine position. The pin-prick test was used for assessment of the level of sensory block every 2 min. The operation began after the sensory block level reached above Th6. Parturients with inadequate spinal anaesthesia or persistent hypotension (systolic blood pressure <90 mmHg) despite ephedrine given by the venous route were eliminated from the clinical trial.

After foetal delivery, different doses of dexmedetomidine (dexmedetomidine, Jiangsu Hengrui Medicine Co. Ltd, Lianyungang, China) diluted with normal saline to 4 μg mL⁻¹ were infused for 10 min as a loading dose. Immediately after the loading dose, maintenance was kept at a dose of 0.3 μg kg⁻¹ h⁻¹ in all parturients. The loading dose of dexmedetomidine for each parturient was determined by the sedation status of the preceding parturient. In the case of adequate sedation, the dose of loading dexmedetomidine was decreased by 0.1 μg kg⁻¹ in the following parturient. An inadequate level of sedation was followed by a 0.1 μg kg⁻¹ increase in loading dexmedetomidine for the subsequent parturient. The initial loading dose for the first parturient was 1.0 μg kg⁻¹ based on our clinical experience. Sedation status was assessed with the Ramsay sedation scale (RSS: 1, anxious and agitated; 2, cooperative and tranquil; 3, drowsy but responds to command; 4, asleep but responds to tactile stimulation and 5, asleep and no response). Adequate sedation was defined as RSS 3 or RSS 4. RSS 5 was defined as over sedation. The sedation status at 5 min after the loading dexmedetomidine was assessed by a researcher blind to the loading doses. The surgeons and parturients were also blind to the loading doses of dexmedetomidine. Hypotension was treated with intravenous fluid and 10 mg ephedrine, which could be repeated every 5 min. Bradycardia defined as a heart rate less than 45 beat·min⁻¹ was treated with 0.5 mg atropine by the venous route.

The primary outcome was the ED50 of dexmedetomidine. The up-and-down method needed at least six success-failure pairs for statistical analysis. The number of patients had to be increased if fewer than six success-failure pairs appeared (11, 12).

Statistical analysis

Statistical analysis was conducted using SPSS 21.0 (IBM SPSS, Armonk, NY, USA). Probit regression analysis was performed to calculate the ED50 and ED95 of the loading dexmedetomidine to obtain adequate sedation at 5 min after the loading dose, as well as when maintenance infusion was done for 5 min.

Results

Twenty eight parturients were included, and 25 completed the study to obtain six pairs of success-failure combinations. The demographic and procedural data are listed in Table 1. Three parturients were removed from the study due to one case each of inadequate spinal anaesthesia, persistent hypotension and patient refusal.

The ED50 and ED95 of the loading dexmedetomidine to achieve RSS ≥3 at 5 min after the loading dose were estimated to be 0.82 μg kg⁻¹ (95% confidence interval [CI] 0.73–0.89 μg kg⁻¹) and 0.96 μg kg⁻¹ (95% CI 0.90–1.39 μg kg⁻¹). No RSS score of 5, which was taken as over sedation, was detected (Figure 1).

The ED50 and ED95 of the cumulative dose (the sum of the loading dose and the maintenance dose [0.025 μg kg⁻¹]

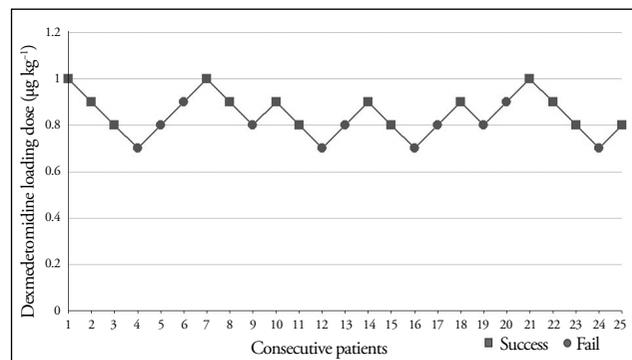| Table 1. The patients' characteristics and surgical data (n=25)	
Age (years)	31.1±6.5
Weight (kg)	67.1±7.3
Height (cm)	161.3±5.4
Operation duration (min)	41.9±8.3
Data are presented as the mean ± standard deviation.	

Figure 1. The sedation effect of different loading doses of dexmedetomidine in 25 consecutive parturients undergoing caesarean section under spinal anaesthesia

Table 2. Ephedrine use, atropine use and adverse effects

	The success group (n=14)	The fail group (n=11)	p
Ephedrine	6 (43%)	5 (45%)	1.00
Atropine	3 (21%)	2 (18%)	1.00
Hypotension	6 (43%)	5 (45%)	1.00
Bradycardia	3 (21%)	2 (18%)	1.00
Dizziness	3 (21%)	1 (9%)	0.60
Nausea	3 (21%)	2 (18%)	1.00

Values are presented as number of patients (percentage). Fisher's exact test was used to compare the variables between the two groups. A value of $p<0.05$ was considered significant.

for the following 5 min) until 5 min after the loading dose to achieve adequate sedation were 0.85 µg kg^{-1} and 0.99 µg kg^{-1}, respectively.

No significant difference was found in ephedrine use, atropine use, or adverse effects between the success group and the fail group (Table 2).

Discussion

Only 1 out of 28 parturients was excluded for inadequate anaesthesia. This demonstrates that low-dose bupivacaine (≤8 mg) and 75 µg fentanyl provide sufficient anaesthetic conditions for spinal anaesthesia for caesarean section. This is in line with Lee's study (13). According to the result of this study, the ED50 and ED95 of loading dexmedetomidine to achieve adequate sedation at 5 min after the loading dose are 0.82 µg kg^{-1} and 0.96 µg kg^{-1}, respectively, with the same method of spinal anaesthesia.

The result of this study is consistent with the previous studies of Ok et al. (6) and Song et al. (4) that indicate that 1 µg kg^{-1} loading dexmedetomidine and a low maintenance infusion after that can result in adequate sedation with minimal hemodynamic instability and without delayed recovery. Pollock et al.(9) and Gentili et al. (10) work showed that spinal anaesthesia can cause sedation that can last for 1 hour. In this study, the ED50 and ED95 of the loading dexmedetomidine were calculated with the same method of spinal anaesthesia, so the ED50 and ED95 of this study are only meaningful for this type of spinal anaesthesia.

The sedation status was evaluated during the initial 15 min, and the dose-response effect in the following time was not determined in this clinical trial. Lee et al. (14) used a similar administration method and found that the maximal sedation status was at 45 min after the start of the loading dexmedetomidine and that there was a peak level in plasma soon after completion of the loading dexmedetomidine. In clinical practice, it is necessary to achieve adequate sedation status within 10–20 min and after that to adjust the maintenance dose according to the effect on the parturients. Although the maximal sedation effect of dexmedetomidine is not observed in the initial 15 min, this time interval is long enough to achieve adequate sedation for anxious parturients while still allowing mother-infant bonding after foetal delivery.

The major advantage of the up-and-down method is that the sample size can be decreased to far below the traditional level (11). However, the data obtained from the up-and-down method tends to distribute around the ED50, not as a mode of linear regression, so we applied probit regression to calculate the ED50 and ED95, especially the ED95, which is more precise when calculated this way (11, 12).

There are some limitations to our study. The ED50 and ED95 causing adequate sedation at 5 min after loading dose in the present study are applicable only when the maintenance dose is 0.3 µg kg^{-1} h^{-1}. When the maintenance dose changes, the ED50 and ED95 of the loading dose will also change. As another limitation, the result of this study is suitable to parturients only. What is more, the possible difference between sedation depth and vital signs could not be statistically analysed because of the small sample numbers of participants in the success group and the fail group. In addition, we decided the loading dose based on pregnancy weight because this is an easy value to obtain. However, after foetal delivery, the weight of parturients will decrease, and this will result in inaccuracy.

Conclusion

The ED50 and ED95 of loading dexmedetomidine to obtain adequate sedation for caesarean section under spinal anaesthesia with low dose bupivacaine and fentanyl are 0.82 µg kg^{-1} and 0.96 µg kg^{-1}, respectively.

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