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Original article

Potential risk factors for dexmedetomidine withdrawal seizures in infants after surgery for congenital heart disease

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Abstract

Purpose: Few studies are available on withdrawal seizures about dexmedetomidine (DEX). Thus, we retrospectively evaluated the incidence of withdrawal seizures after discontinuation of DEX and examined potential risk factors in infants after cardiovascular surgery.

Methods: The medical records of 142 infants who had undergone cardiovascular surgery between April 2010 and November 2013 were examined. Clinical characteristics and usage of DEX were analyzed. DEX withdrawal seizures were evaluated using Withdrawal Assessment Tool – version 1 (WAT-1). All the patients and controls were categorized according to DEX discontinuation strategy, which was either gradual or abrupt.

Results: Nine patients (6.3%) developed generalized clonic or generalized tonic–clonic seizures accompanied by preceding fever of >38 °C approximately four to eight hours following the discontinuation of DEX, and were clinically diagnosed as DEX withdrawal seizures with a median WAT-1 score of 3. Clinical characteristics and operative data were similar, but median cumulative dose and maximum temperature after discontinuation of DEX were significantly higher in infants with withdrawal seizures than in those without ($P = 0.007$ and $P < 0.001$, respectively). Eight of the 9 patients with withdrawal seizures (88.9%) and 20 of the 133 patients (15.0%) with no withdrawal seizures had discontinued DEX abruptly ($P < 0.001$). Cumulative dose and abrupt discontinuation of DEX were significantly associated with DEX withdrawal seizures in infants after cardiovascular surgery ($R = 0.619$, $P = 0.004$).

Conclusions: Physicians should be aware that infants who received DEX after cardiovascular surgery had potential to cause withdrawal seizures accompanied by preceding pyrexia after discontinuation of DEX. Higher cumulative dose and abrupt discontinuation of DEX appears to increase the risk for these withdrawal seizures.

Keywords: Dexmedetomidine; Infant; Seizure; Withdrawal; Congenital heart disease

1. Introduction

Dexmedetomidine (DEX) is a potent and highly selective α2-adrenergic receptor agonist that provides sympatholytic, sedative, amnesic and analgesic properties with minimal respiratory depression [1]. As a result it has become widely used in critically ill children as a

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means of attenuating postoperative emergence complications and managing hemodynamic disturbances after cardiovascular surgery in the intensive care unit (ICU) [2,3].

The manufacturers of DEX warn of the possibility of nervousness, agitation, headache and hypertension if the drug is abruptly discontinued after prolonged administration [4,5]. A number of pediatric studies have reported that tachycardia and hypertension occurred within a few hours of discontinuation of DEX [5,6]. Though, few studies are available on withdrawal seizures about DEX, we have experienced infants who developed generalized clonic or generalized tonic–clonic seizures accompanied by preceding pyrexia on discontinuation of DEX after cardiovascular surgery. Therefore, our primary objective was to establish the incidence of withdrawal seizures in infants treated with DEX as sedative after cardiovascular surgery in our hospital, and evaluate factors associated with the their occurrence, by means of a retrospective analysis of patient records.

2. Methods

This single-center study was conducted at Kagoshima University Hospital, Japan, having been reviewed and approved by the Kagoshima University Ethics Committee, which waived the need for informed consent. We retrospectively analyzed the data of patients who had received a continuous infusion of DEX as a postoperative sedative in the ICU after cardiovascular surgery for congenital heart disease between April 2010 and November 2013. We recorded each patient's age, sex, weight, primary diagnosis, cardiovascular surgical procedure and residual right to left shunt after surgery. Maximum dose, cumulative dose and duration of DEX, use of other sedatives and the depth of sedation measured on the State Behavioral Scale (SBS) score, were also recorded [7]. Patients with preexisting brain abnormalities, history of stroke, hypoxic ischemic encephalopathy, febrile seizure and epilepsy were excluded. None of the patients had received anti-seizure drugs. We categorized the DEX tapering schedule as gradual or abrupt, defining gradual discontinuation as tapering of the dose by 0.1 $\mu g\,kg^{-1}\,h^{-1}$ every 12–24 h with subsequent weaning over several days [8] for a target discontinuation dose of dexmedetomidine of 0.1–0.2 $\mu g\,kg^{-1}\,h^{-1}$ regardless of DEX dosage, and abrupt discontinuation as a sudden discontinuation more than 0.4 $\mu g\,kg^{-1}\,h^{-1}$ without reducing gradual. None of the patients had received enteral clonidine alternative to abrupt discontinuation of DEX [9]. Patients were also given low doses of midazolam (0.05–0.1 $mg\,kg^{-1}\,h^{-1}$) or fentanyl (0.5–1.0 $\mu g\,kg^{-1}\,h^{-1}$), as necessary; however, these were discontinued for more than 24 h before discontinuation of DEX. Physiological data (for example blood pressure, heart rate and peripheral oxygen saturation) were recorded from the bedside monitors in the ICU. Vital signs derived from the monitors were validated and recorded approximately every minute. Considerable DEX withdrawal seizures on discontinuation of DEX were clinically diagnosed and assessed using the Withdrawal Assessment Tool – version 1 (WAT-1) from the data in the medical record retrospectively, and withdrawal events were identified as a WAT-1 score of $\geqslant 3$ [10].

2.1. Statistical analysis

Continuous variables are reported as median values with interquartile ranges (IQR; 25–75th percentiles). Categorical variables are presented as frequencies and proportions. Baseline comparisons between patients were performed using the Mann–Whitney U test or χ^2 analysis (with Yates' correlation or Fisher's exact test as appropriate). A stepwise regression analysis was performed to identify the factors for DEX withdrawal seizures in infants after cardiovascular surgery. All statistical analyses were performed using SPSS statistics software (version 17-0 J, SPSS Japan Inc., Tokyo, Japan). Two tailed P values <0.05 were considered statistically significant.

3. Results

3.1. Baseline characteristics

During the study period, 142 infants with congenital heart disease underwent cardiovascular surgery. Their median age and weight were 3.4 months and 4.5 kg. Patients received a postoperative DEX infusion; their clinical characteristics are shown in Table 1. Median maximum dose, cumulative dose and duration of DEX were 1.5 $\mu g\,kg^{-1}\,h^{-1}$, 39.3 $\mu g\,kg^{-1}$ and 132.0 h, respectively. Median SBS score was −2.

3.2. Withdrawal seizures after discontinuation of dexmedetomidine

Nine patients (6.3%) developed generalized clonic or generalized tonic–clonic seizures accompanied by preceding fever of >38 °C approximately four to eight hours after discontinuation of DEX. These seizures were similar to those found in febrile seizures and were clinically diagnosed as DEX withdrawal seizures with a median WAT-1 score of 3 [interquartile ranges (IQR) 3–4]. The components of the factor of WAT-1 of these 9 patients were as follows; (1) information from patient record, previous 12 h (temperature > 37.8 °C (100%), any loose/watery stools (33.3%), any vomiting/wretching/gagging (22.2%)), (2) 2 min pre-stimulus observation (state of SBS $\geqslant +1$ (33.3%), any sweating (77.8%)), (3)