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Original Article

Effects of dexmedetomidine on cellular immunity of perioperative period in children with brain neoplasms

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Abstract: Objective: To study the effects of dexmedetomidine (Dex) on cellular immunity during the perioperative period in children with brain neoplasms. Methods: Forty children with brain neoplasms scheduled for selective operation were recruited and divided randomly into two groups. The Dex group was given a loading dose of 1 μg*kg^{-1} Dex 15 minutes before anesthesia induction followed by a continuous infusion of 0.5 μg × kg^{-1} × h^{-1} Dex. Patients in control group received a same volume of normal saline for a same time period. Venous blood was collected before anesthesia (T_0), 1 h after operation started (T_1), immediately after operation ended (T_2), 1 day after operation (T_3) and 3 days after operation (T_4), respectively. Results: CD_3^+, CD_4^+, CD_4^+/CD_8^+, NK and B cells at T_1-T_3 decreased significantly ($P < 0.05$) in both groups compared with those at T_0, while the decrease of CD_3^+, CD_4^+, CD_4^+/CD_8^+ and NK cells at T_1-T_3 and B cells at T_1-T_2 in Dex group was significantly less than the control group ($P < 0.05$). All values at T_4 recovered to the level before anesthesia in both groups. Conclusion: Dex given by a continuous intravenous infusion during general anesthesia may effectively inhibit the stress responses and reduce the inhibition of cellular immunity in children with brain neoplasms during the perioperative period.

Keywords: Dexmedetomidine, brain neoplasms, T lymphocyte, NK cells, B lymphocyte

Introduction

Patients with tumors have immune function deficiency, in whom cellular immunity is inhibited by the stimulation and anesthesia during the perioperative period. Moreover, cellular immunity is closely related to infections after operation, wound healing and especially tumor metastasis [1]. So it's significantly important to study the effect of anesthesia on immune function in patients with tumors. It was reported that dexmedetomidine (Dex), a new α2-adrenergic receptor agonist, could improve the cellular immunity of perioperative period and reduce the possibility of hematogenous metastasis [2, 3]. However, no definite conclusion about the influence of perioperative cellular perioperative in children with tumors has been made at home and abroad. This study was to evaluate effects of Dex on immune function in children with brain tumors during perioperative period, in order to provide reference of drug usage of anesthesia.

Materials and methods

General data

The study was ratified by Ethics Committee of Putuo District people's Hospital, and informed consents were signed by guardians of all patients. Forty patients (gender: 23 boys, 17 girls; age: 8 months-14 years; weight: 7-32 kg, ASA I-II) with brain neoplasms (including glioma, V-P shunt, meningioma and so on) were recruited, among whom there was no history of malnutrition, immune deficiency, diabetes, chronic obstructive pulmonary diseases, pneumonia or radiotherapy. Patients were allotted into Dex group and control group with a double-blind randomized method.

Anesthesia regimen

Patients in both groups were routinely given an intramuscular injection of atropine of 0.01-0.02 mg.kg^{-1} 30 minutes before operation. ECG, oxygen saturation and noninvasive blood pressure

Table 1. Comparisons of general condition and operative conditions of patients in two groups

Factors	Dex (n = 20)	Control (n = 20)	T	*P* value
Age (years)	5.81 ± 2.7	5.69 ± 3.5	1.97	0.056
Weight (kg)	16.5 ± 7.4	17.2 ± 8.1	-2.113	0.061
Operation time of duration (min)	135.7 ± 32.8	136.6 ± 41.7	-1.234	0.225
Anesthesia time of duration (min)	157.3 ± 29.3	159.2 ± 37.8	-1.756	0.087

(BP) were monitored after patients entered the operating room. The right internal jugular venous pathway was accessed, and intravenous infusion of lactated Ringer's solution of 6-8 mL × kg^{-1} × h^{-1} was given. Every patient in Dex group was given a loading dose of Dex (Lot number: 14060332, Jiangsu Hengrui Medicine Ltd.) of 1 μg × kg^{-1} 15 minutes before anesthesia induction followed by a continuous infusion of Dex of 0.5 μg × kg^{-1} × h^{-1} until operation ended, and patients in the control group were given the same volume of normal saline for the same time period. Induction of anesthesia included intravenous injections of remifentanil of 2 μg × kg^{-1}, propofol of 1.5 mg × kg^{-1} and vecuronium bromide of 0.1 mg × kg^{-1}, orotracheal intubation and mechanical ventilation (tidal volume: 10 Ml × kg^{-1}, frequency: 20-22 per minute, Ret CO_2: 25-30 mmHg). Maintenance of anesthesia included inhalation of 2.0%-3.0% sevoflurane, intravenous infusion of propofol of 4-6 mg × kg^{-1} × h^{-1} and remifentanil of 0.2-0.3 μg × kg^{-1} × min^{-1} and intermittent injections of cisatracurium of 0.25 mg × kg^{-1}.

BP and heart rate were maintained by adjusting concentration of sevoflurane, and fluctuated within ± 120% of baseline values. All patients were given compound sodium lactate Ringer's solution and 6% hydroxyethyl starch solution of 15 mL × kg^{-1} respectively. Patients using blood or blood product during operations were excluded from this study.

Observed indicators

2 ml venous blood were collected from each patient with vacuum heparin-anticoagulated tubes before anesthesia (T_0), 1 h after operation started (T_1), immediately after operation ended (T_2), 1 day after operation (T_3) and 3 days after operation (T_4). Blood samples were anticoagulated and tested by flow cytometer (FACSCalibur, BD company, USA) to count T lymphocytes subsets (CD_3^+, CD_4^+, CD_8^+), natural killer cells (NK) (CD_{56}^+) and B lympocytes (CD_{19}^+).

Statistical analysis

Data were analyzed by SPSS11.0. Measurement data were shown as means ± standard deviation, t test was adopted for comparisons general condition and operative conditions of patients in two groups. One-way ANOVA was used to compare each parameter in two groups. Dunnett-t test was applied within the group and LSD-t test was used between two groups, and $P < 0.05$ indicated significant difference.

Results

Consistency Test

Independent-sample T test demonstrated that there were no significant differences between two groups in terms of age, weight, anesthesia time and operation time (**Table 1**).

Comparison of T cell subsets, NK cells and B cells at all times

One-way ANOVA, Dunnett-t test analysis revealed that CD_3^+, CD_4^+, CD_4^+/CD_8^+, NK and B cells at T_1-T_3 decreased significantly compared with those at T_0 in both groups ($P < 0.05$). All values at T_4 recovered to the level (**Table 2**; **Figure 1**).

LSD-t test was applied to compare each parameter in two groups. And the results showed that CD_3^+, CD_4^+, CD_4^+/CD_8^+, NK and B cells at T1-T3 decreased more significantly in the control group compared with the Dex group ($P < 0.05$). All values at T_4 recovered to the level (**Table 3**).

Discussion

Cellular immunity, also named T lymphocyte immunity, is overall reflected by $CD3^+$ which is the symbol of antigen expressing of all mature T cells [4]. CD_4^+ T cells are T helper cells, playing a role in assisting induction of cellular immunity and humoral immunity [5]. CD_8^+ T cells are mainly immunosuppression cells, inhibiting functions of other immune cells. Great decrease of ratio of CD_4^+/CD_8^+ usually indicates severity and poor prognosis of diseases [6]. NK cells are main innate immune cells of human body, regulating T cells, B cells and bone marrow stem cells, thus it is important to test NK cells of

Table 2. Comparison of T cell subsets, NK cells and B cells at all times

Factors	Group	T_0	T_1	T_2	T_3	T_4
CD_3^+	Dex	63.76 ± 6.35	54.38 ± 4.10*	58.45 ± 6.76*	60.35 ± 6.21*	62.65 ± 7.25
CD_4^+		34.68 ± 4.54	25.17 ± 3.35*	27.08 ± 6.62*	30.87 ± 6.34*	34.54 ± 7.65
CD8		22.10 ± 5.64	22.76 ± 2.64	22.92 ± 7.54	22.43 ± 5.62	22.19 ± 6.62
CD_4^+/CD_8^+		1.56 ± 1.12	1.11 ± 0.89*	1.18 ± 1.02*	1.37 ± 0.37*	1.52 ± 1.08
NK cells		18.82 ± 6.13	12.15 ± 2.78*	16.78 ± 5.13*	18.49 ± 3.84*	19.47 ± 4.44
B cells		11.12 ± 4.37	7.45 ± 2.43*	7.61 ± 3.22*	7.65 ± 2.59*	9.34 ± 3.51
CD_3^+	Control	62.71 ± 7.73	44.12 ± 3.85*	47.34 ± 4.88*	54.28 ± 6.58*	60.97 ± 5.32
CD_4^+		35.73 ± 5.65	17.82 ± 5.34*	21.35 ± 4.07*	22.76 ± 6.23*	34.38 ± 6.27
CD8		23.15 ± 5.83	24.89 ± 7.92	24.76 ± 7.46	23.42 ± 5.67	23.48 ± 5.72
CD_4^+/CD_8^+		1.54 ± 1.08	0.72 ± 0.48*	0.86 ± 0.47*	0.97 ± 0.24*	1.48 ± 1.12
NK cells		17.71 ± 4.20	5.13 ± 2.21*	11.54 ± 2.03*	13.17 ± 3.28*	17.69 ± 3.21
B cells		11.38 ± 4.72	5.10 ± 3.43*	5.27 ± 2.95*	6.36 ± 2.18*	9.67 ± 4.22

Footnote: *Compared to T0, $P < 0.05$.

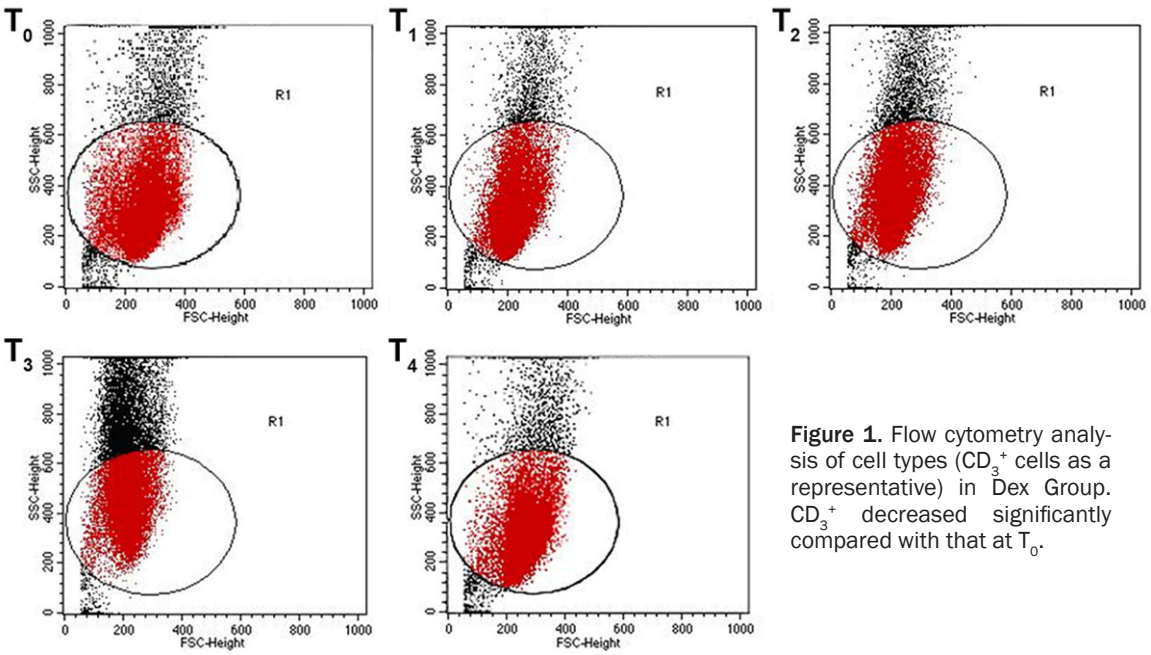

Figure 1. Flow cytometry analysis of cell types (CD_3^+ cells as a representative) in Dex Group. CD_3^+ decreased significantly compared with that at T_0.

patients with tumors to evaluate the genesis, development and prognosis of diseases [7].

Bar-Yosef et al [8] reported that neuroendocrine reactions caused by operative stress could cause inhibition of cellular immunity, thus raising the posibility of tumor metastasis during perioperative period. This study showed that T cell subsets, NK cells and B cells in peripheral venous blood decreased 1 hour after operation started, immediately after operation ended and 1 day after operation, and increased to the original level till 3 days after operation (**Table 2**), indicating that anesthesia could inhibit cellular immunity in patients with brain neoplasms surgeries, which was in accordance with the early reported study.

As for the reason, patients with tumors usually have insufficient cellular immune function: activities of T cell subsets and NK cells in peripheral blood are diminished significantly. Perioperative state, anesthesia methods, anesthetics, operative trauma, pain and hypotension, hypothermia, blood transfusion and hyperglycemia during operation could impact immune function, causing further inhibition of anti-tumor immunity [9]. In other words, opera-

Table 3. The comparison of T cell subsets, NK cells and B cells at all times between two groups ($\bar{x} \pm S$)

	D (n = 20)					C (n = 20)				
	T_0	T_1	T_2	T_3	T_4	T_0	T_1	T_2	T_3	T_4
CD_3^+	63.76 ± 6.35	54.38 ± 4.10*	58.45 ± 6.76*	60.35 ± 6.21*	62.65 ± 7.25	62.71 ± 7.73	44.12 ± 3.85	47.34 ± 4.88	54.28 ± 6.58	60.97 ± 5.32
CD_4^+	34.68 ± 4.54	25.17 ± 3.35*	27.08 ± 6.62*	30.87 ± 6.34*	34.54 ± 7.65	35.73 ± 5.65	17.82 ± 5.34	21.35 ± 4.07	22.76 ± 6.23	34.38 ± 6.27
CD8	22.10 ± 5.64	22.76 ± 2.64	22.92 ± 7.54	22.43 ± 5.62	22.19 ± 6.62	23.15 ± 5.83	24.89 ± 7.92	24.76 ± 7.46	23.42 ± 5.67	23.48 ± 5.72
CD_4^+/CD_8^+	1.56 ± 1.12	1.11 ± 0.89*	1.18 ± 1.02*	1.37 ± 0.37*	1.52 ± 1.08	1.54 ± 1.08	0.72 ± 0.48	0.86 ± 0.47	0.97 ± 0.24	1.48 ± 1.12
NK cells	18.82 ± 6.13	12.15 ± 2.78*	16.78 ± 5.13*	18.49 ± 3.84*	19.47 ± 4.44	17.71 ± 4.20	5.13 ± 2.21	11.54 ± 2.03	13.17 ± 3.28	17.69 ± 3.21
B cells	11.12 ± 4.37	7.45 ± 2.43*	7.61 ± 3.22*	7.65 ± 2.59*	9.34 ± 3.51	11.38 ± 4.72	5.10 ± 3.43	5.27 ± 2.95	6.36 ± 2.18	9.67 ± 4.22

Footnotes: *Compared to control, $P < 0.05$.

tion trauma and anesthesia aggravate the inhibition of immunity, which is mediated by multiple neuroendocrinal pathways, including opiates, hypothalamic-pituitary-adrenal axis hormones, secretion and release of catecholamine [10]. All these substances can cause decreased numbers and activities of T and NK cells, which in turn inhibit cellular immunity of human body [10]. Inhaled anesthetics, such as halothane, sevoflurane and isoflurane, can inhibit lymphocytes proliferation, induce apoptosis of lymphocytes and inhibit activities of NK cells in a dose-related way, which promotes the tumors metastasis [11]. Intravenous anesthetics propofol can decrease release of IL-8 from neutophils, inhibit phosphorylation of p42 mitogen activated protein kinase, damage chemotaxis and phagocytosis of mononuclear macrophages and diminish secretion of IFN-a induced by lipopolysaccharide [12, 13]. Opiodis can decrease proliferation of T lymphocytes, actives of NK cells and phagocytosis of macrophages and reduce production of IL-2 and IFN-1 [14]. All these factors mentioned above make the inhibition of cellular immunity during perioperative period an important cause of tumors metastasis and spread after operation.

Dex is a new α_2-adrenergic receptor agonist, which has pharmaceutical characteristics of inhibiting sympathetic activities and relieving stress reaction [15]. It was indicated that adults had improved cellular immunity during perioperative period, when receiving a loading dose of intravenous Dex of 1 $\mu g \times kg^{-1}$ for 10 minutes followed by a constant intravenous infusion of Dex of 0.5 $\mu g \times kg^{-1} \times h^{-1}$ till operation ended [16]. It was considered that α_2-adrenergic receptor agonists had dual effects on regulating stress reactions of human body, increasing peripheral local tumor cell apoptosis and anti-inflammatory factors, besides analgesic effect through inhibiting central neutral system [17]. As for the effects of Dex on cellular immunity in children with brain neoplasms, there was still no definite conclusion at home and abroad.

The operative anesthesia of infants is special, due to young age, light weight, general complications of malnutrition at different degrees, immaturity of organs and poor compensation abilities. The functions of heart, lung and coagulation can be greatly affected by release of stress hormone, raise of inflammatory factors, hyperglycemia and hyperlactacidemia during perioperative period caused by operative stress and anesthesia, which can lead to reperfusion injury of heart and lung, multiple organs injuries and even failures. So it is important to modulate the stress reaction moderately to make young patients get through perioperative period safely. This study demonstrated that a proper dose of Dex given to patients with surgeries of brain neoplasms could affect peripheral T cell subsets, NK cells and B cells 1 hour after operation started, immediately after operation ended and 1 day after operation, indicating that using α_2-adrenergic receptor agonist such as Dex could relieve inhibition of immunity while reducing stress reactions in children with brain neoplasms surgeries. The possible reasons that Dex can improve cellular immunity are as follows: 1) Dex depresses sympathetic activities and serum concentration of catecholamine and further alleviate operative stress and its coupling immunity inhibition by activating on the a_2-adrenergic receptors with high selectivity in central and peripheral nerve system [18]; 2) Dex can decrease usage of opioids during and after operations, thus reducing the inhibition of immunity caused by opioids [19]; 3) Dex was infused before anesthesia, so analgesia formed before operative traumatic irritations, which prevented the sensitization of central and peripheral nerves, reduced pain caused by traumatic irritations and achieved preemptive analgesia. The specific mechanisms of Dex in improving cellular immunity are not clear yet, which needs to be further studied.

In conclusion, Dex, used in anesthesia of neurosurgical operations, was helpful for children with brain neoplasms to reduce the stress reactions, relieve inhibition of immunity during perioperative period and recovery after operations.

Disclosure of conflict of interest

None.

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