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Original Article

Effects of dexmedetomidine on plasma glucose, cortisol and adrenocorticotropic hormone concentrations of canine undergoing ovariohysterectomy

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Abstract

To study the effect of dexmedetomidine on plasma glucose, cortisol and adrenocorticotropic hormone concentrations in canine undergoing ovariohysterectomy, 24 beagles were divided into 3 groups randomly. Group A was intramuscularly injected with 2 ml of saline 10 min after surgery. Group B was intramuscularly injected with 20 μg/kg of dexmedetomidine 10 min before surgery. Group C was intramuscularly injected with 20 μg/kg of dexmedetomidine 10 min after surgery. Two milliliters of blood was collected at 3 h, on the second day and on the third day after surgery. Plasma glucose, cortisol and adrenocorticotropic hormone concentrations were measured. The study showed that dexmedetomidine significantly decreased the plasma glucose concentration of the dogs. The treatment with dexmedetomidine before surgery could not decrease the adrenocorticotropic hormone concentration significantly. Intramuscularly injecting dexmedetomidine (20 μg/kg) at 10 min after surgery decreased the levels of plasma glucose, cortisol and adrenocorticotropic hormone of the canine undergoing ovariohysterectomy. Therefore, dexmedetomidine could be a good choice for avoiding stress response of surgery.

Keywords: hyperglycemia, stress response, beagles, surgery

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Introduction

Stress response of surgery is the name given to the hormonal and metabolic changes following injury or trauma and it causes organ damage (Rivers et al., 2001). Dexmedetomidine (DEX), which is widely used in the process of operation, can enhance the vagus nerve excitability and hemodynamic stability and reduce the dosage of anesthetic with sedation and analgesia. DEX has no depressant effects on ventilation, thus its analgesic effect may offer a significant advantage for patients at risk of respiratory decompensation (Yacout et al., 2012).

Hyperglycemia is well thought as a normal metabolic stress response (McCowen et al., 2001). In settings of injury, it has been named stress-induced hyperglycemia (SIH). The cause of SIH is the overabundance of glucose production or a state of enhanced glucose production, resulting in increase in stress hormones and cytokines (Epstein and Breslow, 1999).

Adrenocorticotropic hormone (ACTH), which is often produced in response to biological stress, is an important component of the hypothalamic-pituitary-adrenal axis. Increased production and release of cortisol by the cortex of the adrenal gland are the important effects of ACTH (Dibner et al., 2010). During stress, excitation of the hypothalamus results in secretion of ACTH which initiates sudden increase in cortisol level sequentially. The stressful state can be overwhelmed by the metabolic effects of cortisol directly. The metabolism and utilization of glucose are affected by cortisol in hepatic and extra-hepatic tissues (Yacout et al., 2012). Increase in ACTH results from the stimulation of the anterior pituitary by the hypothalamic releasing factors during operation (Lyons and Meeran, 1997). In turn, the adrenal cortical secretion of glucocorticoids can be stimulated by ACTH, thus contributing to elevation of the serum levels of cortisol. There is an intense relation between cortisol and ACTH levels (Krinsley, 2006).

The aims of the present work were to study the effect of DEX on plasma glucose, cortisol and ACTH concentrations in canine undergoing ovariohysterectomy and to discover if DEX is a good choice for avoiding the stress response of surgery.

Materials and Methods

Animals: After receiving approval from the Shenyang Agricultural University Animal Experimental Board, 24 female Beagles (Sprague Dawley, SD) aged 1 year with mean weight of 7.7±2.2 kg were used in this study. According to clinical examination and blood test, the dogs were considered to be healthy. The animals were fed on commercially available dog food twice a day for 4 weeks. All surgery was performed in the morning. Food was withheld for 12 hours and water was withheld for three hours prior to anesthesia.

Experimental design: The dogs were divided into 3 groups randomly (n=8). The three groups were designated as follows: group A was intramuscularly injected with 2 ml of saline 10 min after surgery, group B was intramuscularly injected with 20 μg/kg of dexmedetomidine 10 min before surgery, and group C was intramuscularly injected with 20 μg/kg of dexmedetomidine 10 min after surgery. Two milliliters of blood was collected at 3 h, on the second day and on the third day after surgery. All analgesics were diluted with saline to a total volume of 2 ml in order to avoid any possible bias. Each dog underwent ovariohysterectomy in which via midline coeliotomy was performed by the same surgeon. The same drug (saline and DEX) was given as initial equivalent dose 24 h and 48 h after surgery in each group.

On the morning of the surgery, a 22-gauge catheter was placed into the cephalic vein of the dog for medication and blood sample collection. Prior to premedication, each animal was assessed, and baseline physiological data were obtained and blood was collected from the catheter. Atropine sulphate (Atropin 2%, China for Fang Qiang Pharmaceutical Co., Ltd) at 0.04 mg/kg was administered subcutaneously approximately 30 min before general anesthesia. Anesthesia was induced by intravenous administration of propofol (PropoVet Multidose, Finland for Orion Pharma) at 5 mg/kg and maintained with inhalation of isoflurane (Isoba vet, China for Schering-Plough A/S) mixed in air at 1.5%.

Two milliliters of blood was collected at 3 h, on the second day and on the third day after surgery (8:00-8:15 am, fasting). The samples were placed into iced water immediately after collection. The samples collected in EDTA tubes were centrifuged at 3000 g for 15 min. Plasma was then frozen at -20℃ until analyses were performed.

Plasma glucose concentration was determined by a blood-gas analyzer (ABL800 Flex, Radiometer) within 1 h of collection. Plasma cortisol concentration was determined by using a radioimmunoassay kit (Coat-A-Count Cortisol assay, Siemens Medical Solutions Diagnostics and Human Insulin-Specific RIA, Millipore). Sensitivity of the assay of cortisol was 5.5 nmol/L. Plasma ACTH concentration was measured by means of the immunoradiometric assay (IRMA) using an available commercial kit (Nichols Advantage ACTH Assay, Nichols Institute Diagnostics, Bad Vilbel, Germany). The intra-assay and inter-assay coefficients of variation for ACTH were 3% and 6.8%, respectively.

Pain scores of all dogs were evaluated using the form of the Glasgow Composite Measure Pain Scale (CMPS-SF; Reid et al., 2007). All pain measurement was performed by one experienced individual who was blind to the treatment of the dogs. CMPS-SF and the procedures of pain evaluation are presented in Table 1. Pain assessment was performed at least two days before pre-medication (baseline), every 2 h for the first 8 h (post-extubation), at 12 h and at 24 h. Post-operative pain behaviors at each time point were measured and the scores were calculated.

Statistical analysis: The SAS 9.3 software (SAS Institute, Cary, NC) was used to analyze the data. All the data were analyzed using the analysis of variance (ANOVA). Paired t-test was used to determine within-group (intragroup) differences while Duncan's multiple range test (DMRT) was used to examine intergroup differences. A value of P < 0.05 denoted significance.

Table 1 Form of the Glasgow composite pain scale

	Descriptor	Score
Category A	(I) quiet	0
	crying or whimpering	1
	screaming	3
	(II) ignoring any wound or painful area	0
	looking at wound or painful area	1
	licking wound or painful area	2
	rubbing wound or painful area	3
	chewing wound or painful area	4
Category B	(III) normal	0
	lame	1
	slow or reluctant	2
	stiff	3
	it refuses to move	4
Category C	(IV) do nothing	0
	look around	1
	flinch	2
	growl or guard area	3
	snap	4
	cry	5
Category D	(V) happy and content or happy and bouncy	0
	quiet	1
	indifferent or non-responsive to surroundings	2
	nervous or anxious or fearful	3
	depressed or non-responsive to stimulation	4
	(VI) comfortable	0
	unsettled	1
	restless	2
	hunched or tense	3
	rigid	4

Results

There were no differences in duration of surgery (A: 38.16 ± 9.24 min; B: 36.72 ± 9.53 min; C: 36.42 ± 8.15 min) and extubation time (A: 9.45 ± 2.26 min; B: 9.34 ± 2.27 min; C: 9.12 ± 2.34 min) among the three groups.

The CMPS-SF pain scores of all dogs in each group are shown in Table 2. Compared with group B, group A had significantly higher CMPS-SF pain scores ($P < 0.05$) at 6, 8 and 12 h. Compared with group A, group C had significantly lower CMPS-SF pain scores ($P < 0.05$) at 2, 4, 6, 8 and 12 h. Compared with group B, group C had significantly lower CMPS-SF pain scores ($P < 0.05$) at 2 and 4 h. However, the CMPS-SF pain scores in group C were not significantly different from those of group B ($P > 0.05$) at 6, 8, 12 and 24 h. The dogs in group A had significantly higher CMPS-SF pain scores at 2, 4, 8 and 12 h than the dogs in group C, but not group B ($P < 0.05$).

Changes in plasma glucose concentration of all the groups are shown in Table 3. There were significant differences between group A and the other groups at 3 h and on the second day after surgery, but not before surgery and on the third day after surgery ($P < 0.05$). The trend of plasma glucose concentration changes in each group (intragroup) was similar. It was shown that there were significant differences between before surgery and the other time points ($P < 0.05$).

Changes in plasma cortisol concentration of all the groups are shown in Table 4. There were significant differences between group A and the other groups at 3 h, on the second day and on the third day after surgery, but not before surgery ($P < 0.05$). The trend of plasma cortisol concentration changes in each group (intragroup) was similar. It was shown that there were significant differences between before surgery and the other time points ($P < 0.05$).

Changes in plasma ACTH concentration of all the groups are shown in Table 5. The plasma ACTH concentration was not significantly different among the groups before surgery and on the third day after surgery ($P < 0.05$). There were significant differences between group A and the other groups ($P < 0.05$), and also between group B and group C at 3 h after surgery. There were significant differences between group A and the other groups on the second day after surgery ($P < 0.05$).

Table 2 Pain assessment scores for Glasgow Composite Measure Pain Scale (CMPS-SF) in each treatment group (mean ± SD)

Group	Time point (h)						
	baseline	2	4	6	8	10	12
A	0.0 ± 0.0	5.2 ± 1.1*	4.3 ± 0.8*	4.4 ± 0.6#	3.1 ± 0.6#	2.2 ± 0.7#	1.3 ± 0.7*
B	0.0 ± 0.0	4.7 ± 1.0*	3.7 ± 0.9*	3.2 ± 0.7*	2.1 ± 0.7*	1.7 ± 0.6*	1.2 ± 0.5*
C	0.0 ± 0.0	3.8 ± 0.7#	2.8 ± 0.6#	2.7 ± 0.8*	1.5 ± 0.8*	1.2 ± 1.0*	1.1 ± 0.6*

*#Different superscript letters within the same line denote significant differences at a given time point, $P < 0.05$.

Table 3 Changes in plasma glucose concentration at different time points in each group (mg/dL, n=8)

Group	Plasma glucose concentration			
	Before surgery	**3 h after surgery**	**Second day after surgery**	**Third day after surgery**
A	87.66 ± 9.64^{Ac}	135.18 ± 15.27^{Aa}	116.36 ± 11.30^{Ab}	94.51 ± 8.37^{Bbc}
B	88.28 ± 9.73^{Ab}	107.45 ± 14.34^{Ba}	95.27 ± 10.65^{Bb}	92.29 ± 9.48^{Bb}
C	85.92 ± 10.85^{Ab}	109.80 ± 13.54^{Ba}	92.75 ± 9.26^{Bb}	94.08 ± 9.52^{Bb}

Note: Mean separation by Turkey's HSD (honest significant difference) and Duncan's multiple range test (DMRT). Means with different superscript letters are significantly different (P < 0.05). Direction of mean separation: upper-case letters (along row or intragroup) and lower-case letters (along column or intergroup).

Table 4 Changes in plasma cortisol concentration at different time points in each group (μg/L, n=8)

Group	Plasma cortisol concentration			
	Before surgery	**3 h after surgery**	**Second day after surgery**	**Third day after surgery**
A	65.82 ± 5.21^{Ad}	132.38 ± 18.89^{Aa}	116.17 ± 12.70^{Ab}	97.64 ± 9.63^{Ac}
B	64.73 ± 6.23^{Ac}	95.56 ± 10.27^{Ba}	88.73 ± 9.35^{Bab}	80.85 ± 8.50^{Bb}
C	65.10 ± 6.18^{Ab}	80.16 ± 8.34^{Ca}	74.64 ± 7.75^{Ca}	81.51 ± 9.46^{Ba}

Note: The statistical analysis symbols are similar to those in Table 3.

Table 5 Changes in plasma adrenocorticotropic hormone concentration at different time points in each group (ng/L, n=8)

Group	Plasma adrenocorticotropic hormone concentration			
	Before surgery	**3 h after surgery**	**Second day after surgery**	**Third day after surgery**
A	3.35 ± 0.31^{Acd}	4.95 ± 0.85^{Aa}	4.24 ± 0.62^{Ab}	3.72 ± 0.40^{Ac}
B	3.48 ± 0.45^{Ab}	4.01 ± 0.72^{Ba}	3.72 ± 0.68^{Bab}	3.69 ± 0.55^{Aab}
C	3.24 ± 0.29^{Aa}	3.52 ± 0.34^{Ca}	3.71 ± 0.48^{Ba}	3.62 ± 0.54^{Aa}

Note: The statistical analysis symbols are similar to those in Table 3.

Discussion

CMPS-SF is used for assessing postoperative pain, mainly through observation of behavior, and is one of the best ways to assess the level of pain. In addition, the use of CMPS-SF has been validated by Murrell et al. (2008). Therefore, CMPS-SF was applied in the present study to assess the level of postoperative pain in dogs undergoing ovariohysterectomy. Based on the CMPS-SF results, 20 μg/kg DEX was found to have good analgesic effect on the dogs after ovariohysterectomy.

ACTH stimulates the adrenal cortex and secretion of glucocorticoids such as cortisol, but has little control over secretion of aldosterone, the other major steroid hormone from the adrenal cortex. ACTH is secreted from the anterior pituitary in response to corticotropin-releasing hormone from the hypothalamus. Corticotropin-releasing hormone is secreted in response to many types of stress and is inhibited by glucocorticoids, making it part of a classical negative feedback loop. Excitation of the hypothalamus during stress results in the secretion of ACTH, which in turn initiates sudden increase in cortisol level. The metabolic effects of cortisol are directed to overcome the stressful state. Cortisol has widespread effects on the metabolism and utilization of glucose, amino acid and fatty acids in hepatic and extra-hepatic tissues. Cortisol causes rapid mobilization of amino acids and fat from their cellular stores, making them immediately available both for energy and synthesis of other compounds including glucose needed by different tissues.

The connection between elevated glucose levels after surgery and intensity of surgical injury has already been described. The higher the glucose levels of the patient, the higher presence of stress hormones and serious injury (McCowen et al., 2001). The study showed that the plasma glucose concentration of all groups was increased significantly at 3 h after surgery, then decreased gradually on the second and third day. DEX decreased the dogs' plasma glucose concentration effectively.

Aho et al. (1992) found that patients receiving DEX had significantly lower intraoperative cortisol levels compared with those who did not receive the drug before surgery. This supports that DEX administration results in lower levels of stress response of surgery. Uyar et al. (2008) found that plasma concentration of cortisol and glucose increased significantly in the placebo group, than in the DEX group. Interestingly, Mukhar et al. (2006) found that DEX did inhibit the hyperglycaemic response to surgery significantly more than placebo, and that it might reflect attenuation of the sympatho-adrenal response. Aantaa et al. (1990) measured cortisol level in patients undergoing minor gynaecologic surgery and found that it was equally increased in saline and DEX groups. Our study showed that if not receiving DEX, the plasma cortisol concentration of the dogs reached the highest value at 3 h after surgery and then decreased gradually, but the values at 3 days after surgery were significantly higher than the values before surgery. DEX could significantly decrease the plasma cortisol concentration of the dogs. It was also found that receiving DEX after surgery was more effective than receiving it before surgery.

Surgery has been recognized as one of the most potent activators of ACTH secretion (Desborough et al., 2000). The present study showed that if not receiving DEX, the ACTH concentration of dogs reached the highest value at 3 h after surgery, then decreased gradually, and returned to the preoperative level at 3 days after surgery. Moreover, it was found that the decreased ACTH and cortisol levels were related to the pain relief effect of DEX, and that receiving DEX before surgery could not decrease the ACTH concentration effectively, whereas receiving DEX after surgery could significantly stabilize the ACTH concentration.

Conclusion

Intramuscularly injecting DEX (20 μg/kg) at 10 min after surgery can decrease the levels of plasma glucose, cortisol and ACTH in canine undergoing ovariohysterectomy. This will be a good choice for avoiding the stress response of surgery.

Acknowledgements

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บทคัดย่อ

ผลของยา dexmedetomidine ต่อระดับความเข้มข้นของ กลูโคส คอร์ติซอล และฮอร์โมน adrenocorticotropic ในสุนัขที่ได้รับการผ่าตัด ovariohysterectomy

หลิน ลี่[1] จิง ดอง[1] ซิ่วจิง เฟน[2] ไบ ลี่[2] ยงปิง เชน[2] จิเชง ชา[2] ฮองแกง แฟน[2]*

การศึกษานี้เพื่อวิเคราะห์ผลของยา dexmedetomidine ต่อระดับของน้ำตาลในเลือด คอร์ติซอล และฮอร์โมน adrenocorticotropic ในสุนัขที่ได้รับการผ่าตัด ovariohysterectomy โดยศึกษาในสุนัข 24 ตัวแบ่งออกเป็น 3 กลุ่ม กลุ่ม A กลุ่มควบคุม ได้รับน้ำเกลือโดยการฉีดเข้ากล้ามเนื้อ 2 มล. 10 นาทีหลังการผ่าตัด กลุ่ม B ได้รับยา dexmedetomidine 20 ไมโครกรัม / กิโลกรัม โดยการฉีดเข้ากล้ามเนื้อ 10 นาทีก่อนการผ่าตัด และ กลุ่ม C ได้รับยา dexmedetomidine 20 ไมโครกรัม / กิโลกรัม โดยการฉีดเข้ากล้ามเนื้อ 10 นาทีหลังการผ่าตัด จากนั้นเก็บตัวอย่าง เลือดปริมาตร 2 มล ที่เวลา 3 ชั่วโมง วันที่สอง และวันที่สามหลังการผ่าตัด ผลการศึกษาพบว่า ระดับน้ำตาลในเลือดของสุนัขลดลงอย่างมีนัยสำคัญ เมื่อได้รับยา dexmedetomidine ในขณะที่การได้รับยา dexmedetomidine ก่อนการผ่าตัด ไม่สามารถลดความเข้มข้นของระดับฮอร์โมน adrenocorticotropic อย่างมีนัยสำคัญ โดยสรุปการให้ยา dexmedetomidine (20 ไมโครกรัม / กิโลกรัม) ฉีดเข้ากล้ามเนื้อ 10 นาทีหลังการผ่าตัด สามารถลดระดับน้ำตาล คอร์ติซอล และ adrenocorticotropic ในสุนัขที่ผ่าตัด ovariohysterectomy ดังนั้น dexmedetomidine อาจจะเป็นทางเลือกที่ดีเพื่อลดความเครียดของสัตว์ในการผ่าตัด

คำสำคัญ: น้ำตาลในเลือดสูง ตอบสนองความเครียด บีเกิล ผ่าตัด

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