Curative effect of minimally invasive surgery on palmar and foot hyperhidrosis and its influence on serum-related cytokines and immunoglobulins

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Abstract. The curative effect of minimally invasive surgery on palmar and foot hyperhidrosis and its influence on serum-related cytokines and immunoglobulins were investigated. Seventy-six patients with palmar and foot hyperhidrosis admitted to Yunnan University Hospital from August 2014 to July 2016 were selected and randomly divided into control group (n=38) and observation group (n=38) using a random number table. Patients in control group received drug therapy, while those in observation group underwent laparoscopic thoracic-4 sympathetic chain combined with thoracic-3 branch amputation. The therapeutic effects of patients in the two groups were compared. The levels of serum C-reactive protein (CRP), interleukin-6 (IL-6), IL-10 and tumor necrosis factor-α (TNF-α) of patients in the two groups were measured by enzyme-linked immunosorbent assay (ELISA) before treatment and at one week after treatment. The levels of immunoglobulin G (IgG), IgA and IgM were detected by immunoturbidimetry. The quality of life (QOL) in patients was evaluated by quality-of-life index (iQOL) before and after treatment. The total effective rate in the observation group was significantly higher than that in the control group (P<0.05). The serum levels of CRP, IL-6, IL-10 and TNF-α of patients in the two groups were higher at one week after treatment than those before treatment (P<0.05), and there were no significant differences between the two groups (P>0.05). At one week after treatment, IgG, IgM and IgA levels of patients in the two groups were remarkably increased (P<0.05), and there were no significant differences between the two groups (P>0.05). After treatment, the iQQL scores of patients in the two groups were significantly decreased, and iQQL score in observation group was decreased more significantly compared with that in control group (P<0.05). Compared with drug therapy, minimally invasive surgery is more effective in the treatment of palmar and foot hyperhidrosis with smaller trauma and inflammatory reaction, and it has less influence on serum immunoglobulin levels, which is conducive to the rehabilitation of patients.

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Introduction

Palmar and foot hyperhidrosis is a common disease caused by excessive activation of the sympathetic nervous system leading to autonomic excessive secretion of head and facial sweat glands thus resulting in the increased sweating (1). The incidence rate of palmar and foot hyperhidrosis is approximately 1.0% in the Western countries. The epidemiological investigation in China displays that the incidence rate is approximately 4.6% in college and secondary school students in Fuzhou.

The corresponding symptoms generally can be found during the elementary school period among patients with palmar and foot hyperhidrosis. Although the disease cannot affect the health and longevity of patients, it causes inconvenience to their work, study and social life, and have a greater impact on their quality of life (2,3). The therapies of palmar and foot hyperhidrosis include internal medicine and surgery. The effect of drug therapy is poor, with greater side effects, and the long-term use is easy to produce immune tolerance, and relapse easily occurs once the drug is discontinued (4). In the 1980s, the clinical application of thoracoscope contributed to the rapid development of the minimally invasive surgery of palmar and foot hyperhidrosis. It has the advantages of small trauma, quick recovery and remarkable curative effect (5).

Minimally invasive surgery was conducted in patients with palmar and foot hyperhidrosis in this study and obtained satisfactory curative effect.

Materials and methods

General information. Seventy-six patients with palmar and foot hyperhidrosis admitted to Yunnan University Hospital from August 2014 to July 2016 were selected and randomly divided into control group (n=38) and observation group (n=38) using the random number table. Inclusion criteria: i) Patients met the diagnostic criteria of primary hyperhidrosis;

Table I. General data of objects of study.

Characteristics	Control group (n=38)	Observation group (n=38)	t/χ^2 value	P-value
Sex (male/female)	24/14	26/12	0.234	0.629
Age (year old)	18-40	18-45		
Average age (year old)	25.36±5.63	25.85±5.73	0.376	0.708
Duration of illness (year)	11.62±2.46	11.25±2.37	0.668	0.506
BMI (kg/m^2)	23.43±3.27	22.87±3.58	0.712	0.479
Severe degree (n, %)				
Mild	4 (10.52)	3 (7.89)	0.001	0.999
Moderate	16 (42.11)	19 (50.00)	0.211	0.645
Severe	18 (47.37)	16 (42.11)	0.053	0.818

ii) patients with main clinical symptoms of much palmar and foot sweating, lasting more than six months, over more than once every week; iii) patients with hyperhidrosis affecting daily activities; and iv) patients signed the inform consent. Exclusion criteria: i) Patients with severe heart, brain, liver or psychiatric disorders; and ii) patients with severe coagulation disorders and drug allergy to the drug. The differences in general data of patients in two groups were not statistically significant (P>0.05) (Table I). The study was approved by the Ethics Committee of Sun Yat-Sen University (Guangdong, China).

Drug therapy. Drug therapy was used in the control group. Before treatment, patients underwent a general physical examination. Patients with a history of drug allergy were excluded, and the range of sweating was measured by the iodine-starch test. Twenty injection sites were designed at each side of the hands and feet (1.0 cm apart). Botulinum toxin type A (100 units) was diluted using 3 ml sodium chloride solution, and subcutaneous injection was conducted according to the designed injection sites (the amount of injection at each injection site was approximately 2.5 units). Attention was paid that the needle was not too deep to prevent the weakening of muscle strength during injection. The condition of patients was closely observed for approximately 30 min after injection to prevent the occurrence of drug allergy.

Surgical therapy. Patients in the observation group underwent laparoscopic thoracic-4 sympathetic chain combined with thoracic-3 branch amputation. Before operation, chest X-ray, electrocardiogram and blood test and urine routine examination were performed to confirm the indication of operation. General anesthesia was performed with intravenous compound single-lumen endotracheal intubation. The patient was in a semi-supine position, with the upper arms reaching approximately 90 degrees to fully expose the bilateral armpits. The sequence of operation was followed by first right and then left. The incision was performed through the third intercostal space (approximately 1 cm length of incision), followed by placement of needle sleeve (Trocar). By adopting single-hole double-channel video thoracoscope, electric coagulation hook was placed. Through the observation by thoracoscope, the location of R3 (the third rib surface sympathetic ganglia) and R4 (the fourth rib surfaces) were determined. An electric coagulation hook was used to cut off the R4 trunk and perform repeated cauterization to ensure complete separation of the nerve stoma; subsequently, approximately 2 cm length was cut along the rib surface to the outside, so as to observe the existence of collateral fibers, and to ensure the amputation. R3 trunk outside was observed for any collateral fibers. If existing, the electric coagulation would break it, and the incision approximately 1.5 cm in length was foreseeingly made to outside, and if it was completely burned was observed, avoiding the damage to the trunk of R3. At the end of the operation, whether active bleeding was observed, and whether the bilateral hands were dry and warm was determined. After the observation by thoracoscope displayed the swell of lungs, endoscope was withdrawn, annular tubes were extracted and the incision was sutured. If the hands and feet were still cold and damp, the complete disconnection of broken ends and collateral branches of sympathetic nerve should be examined again before the withdrawal of the endoscope.

Index detection. Fasting venous blood (3-5 ml) was collected from patients in the two groups before and at one week after treatment, followed by separation and extraction of serum. The levels of serum C-reactive protein (CRP), interleukin-6 (IL-6), IL-10 and tumor necrosis factor-α (TNF-α) in patients were measured by enzyme-linked immunosorbent assay (ELISA), and related kits were provided by Zhejiang Ikon Co., Ltd., Zhejiang, China. The operations were performed strictly according to the instructions. The optical density (OD) value was read at 450 nm of wavelength by a microplate reader (Jiangsu Potebio Co., Ltd., Jiangsu, China), followed by calculation of levels of CRP, IL-6, IL-10 and TNF-α. The levels of immunoglobulin G (IgG), IgA and IgM in patients were detected by immunoturbidimetry, and related kits were provided by Shanghai Yanjin Biotechnology Co., Ltd., Shanghai, China. The operations were strictly performed according to the instructions. The contents of IgG, IgA and IgM in the sample were calculated by measuring turbidity of reaction liquid and comparing with standard samples.

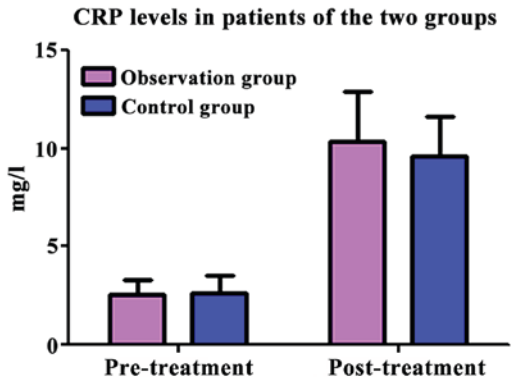

Figure 1. CRP levels in patients of the two groups. Comparisons between pre-treatment and post-treatment in patients of the two groups, P<0.05. Comparisons between two groups before and after treatment, P>0.05.

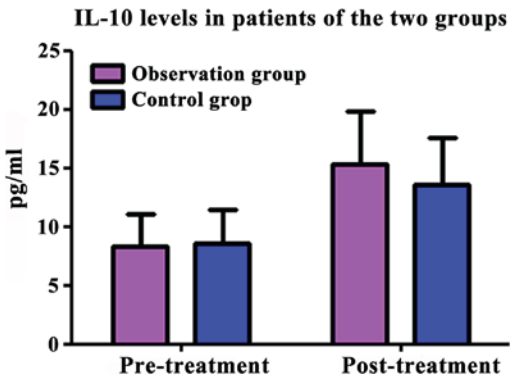

Figure 3. IL-10 levels in patients of the two groups. Comparisons between pre-treatment and post-treatment of patients of the two groups, P<0.05. Comparisons between two groups before and after treatment, P>0.05.

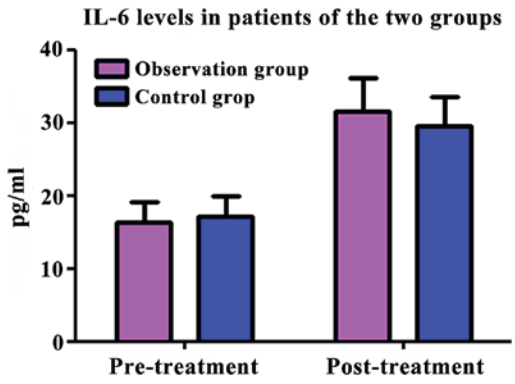

Figure 2. IL-6 levels in patients of the two groups. Comparisons between pre-treatment and post-treatment in patients of the two groups, P<0.05. Comparisons between two groups before and after treatment, P>0.05.

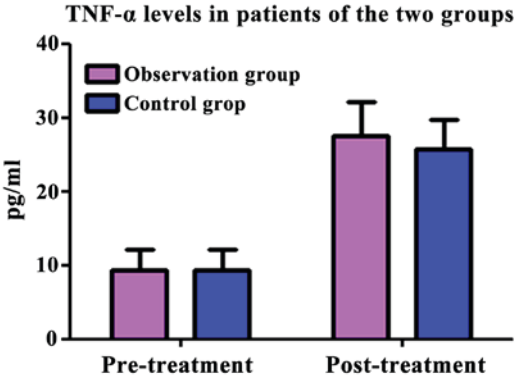

Figure 4. TNF-α levels in patients of the two groups. Comparisons between pre-treatment and post-treatment of patients of the two groups, P<0.05. Comparisons between two groups before and after treatment, P>0.05.

Follow-up. After treatment, follow-up was conducted by outpatient, telephone, network and other methods for 6 months, so as to understand the improvement and recurrence of the primary sweating site and assess the quality of life.

Evaluation criteria. Criteria for judging the severity of palmar and foot hyperhidrosis: a) mild, it was moist when sweating; b) moderate, sweating soaked a handkerchief; c) severe, sweat dropped as beads of sweat.

The curative effect was evaluated, and the criteria were as follows: a) cured, after 3 months of treatment, hands and feet were warm and dry, with no moisture and sweat in the quiet state and suitable room temperature; b) effective, after treatment, the wet and sweating conditions of hand and foot were improved significantly, with slight sweating under normal conditions; c) ineffective, after 3 months of treatment, severe sweating occurred in patients or sweating did not improve significantly compared with that before treatment. Therapeutic total effective rate = cure rate + effective rate.

Fasting venous blood (5 ml) was collected from patients in the morning before and at one week after treatment, followed by separation and extraction of serum and stored at -20˚C. The levels of serum CRP, IL-6, IL-10 and TNF-α in patients were measured by ELISA before treatment and at one week after treatment. The levels of immunoglobulin IgG, IgA and IgM were detected by immunoturbidimetry.

The quality-of-life index (iQOL) was used to assess the quality of life in patients before and after treatment (6). According to the impact of disease on the quality of life in patients, the severity was divided into 0-3 points (0 point indicates no impact on quality of life; 3 points indicate a serious impact on quality of life), and the score was negatively related to the quality of life of patients.

Statistical analysis. Data were processed by SPSS 19.0 (SPSS Inc., Chicago, IL, USA) software. Measurement data were expressed by mean ± standard deviation, and t-test was adopted. Count data were expressed by percentage, and Chi-square test was utilized. The rank sum test was used for curative effect. P<0.05 was considered to indicate a statistically significant difference.

Results

Three months later, the therapeutic effective rate in the observation group was 94.74%, which was significantly higher than 73.23% in the control group, and the difference was statistically significant (P<0.05) (Table II).

Comparisons of levels of CRP, IL-6, IL-10 and TNF-α in the patients of the two groups. Before treatment and at one week after treatment, CRP levels in observation

Table II. Comparison of curative effect in patients of the two groups (n, %).

Group	N	Cured	Effective	Ineffective	Totally effective
Observation	38	27 (71.05)	9 (23.68)	2 (5.26)	6 (94.74)
Control	38	12 (31.58)	16 (42.11)	10 (26.32)	18 (73.23)

The curative effect in two groups is processed by rank sum test, Z=3.590, P<0.001.

Table III. Comparisons of immunological indexes in patients of the two groups (g/l).

	IgA				IgG				IgM			
Group	Before treatment	After treatment	t-value	P-value	Before treatment	After treatment	t-value	P-value	Before treatment	After treatment	t-value	P-value
Observation	1.03±0.26	1.69±0.45	7.828	<0.001	5.15±1.63	9.05±2.67	7.685	<0.001	1.15±0.43	1.83±0.36	7.475	<0.001
Control	1.04±0.27	1.67±0.34	8.945	<0.001	5.17±1.45	9.07±2.42	8.522	<0.001	1.17±0.35	1.88±0.47	7.469	<0.001
t-value	0.164	0.219			0.057	0.034			0.222	0.521		
P-value	0.870	0.827			0.955	0.973			0.825	0.604		

Table IV. iQOL in patients of the two groups.

		iQQL score			
Group	Case	Before treatment	After treatment	t-value	P-value
Observation	38	2.36±0.32	0.41±0.12	35.173	<0.001
Control	38	2.35±0.33	1.18±0.87	7.751	<0.001
t-value		0.134	5.405		
P-value		0.894	<0.001		

group were 2.57±0.24, 10.37±1.23 mg/l; IL-6 levels were 6.43±4.24, 31.67±3.23 pg/ml; IL-10 levels were 8.43±2.24, 15.37±3.23 pg/ml; and TNF-α levels were 9.43±5.24, 27.67±3.23 pg/ml. Before treatment and at one week after treatment, CRP levels in observation group were 2.65±0.35, 9.63±2.15 mg/l; IL-6 levels were 17.24±4.36, 29.58±3.74 pg/ml; IL-10 levels were 8.68±2.58, 13.67±3.23 pg/ml; TNF-α levels were 9.36±5.17, 25.85±4.43 pg/ml. The serum levels of CRP, IL-6, IL-10 and TNF-α in the patients of the two groups after treatment were increased compared with those before treatment (P<0.05). There were no statistically significant differences in patients between two groups (P>0.05) (Figs. 1-4).

Comparisons of immunological indexes in patients of the two groups. After treatment for one week, IgG, IgM and IgA in patients of the two groups were obviously increased (P<0.05). The differences were not statistically significant in patients between two groups (P>0.05) (Table III).

Comparisons of quality of life in patients of the two groups. Through the follow-up for six months, it could be seen that iQOL scores in patients of the two groups were remarkably decreased, which was more significant in observation group (P<0.05) (Table IV).

Discussion

The pathogenesis of palmar and foot hyperhidrosis is not yet entirely clear, and anxiety, stress and hot weather all contribute to this disease. Most studies suggest that it is closely related to the overactivity of sympathetic nerve (7). The secretion of sweat glands in the human body is governed by sympathetic nerves, and the sympathetic nerve chain belongs to the autonomic nervous system, which consists of sympathetic ganglia and intersegmental branches, and is symmetrically distributed on both sides of the human spine (8). The sympathetic nerve, which usually controls the sweat glands of hands and feet, is located at the levels of thoracic-2 to the thoracic-6 spinal segments and controls the sweat glands by releasing acetylcholine (9). Studies have revealed that sympathetic nerve fiber myelin sheath is thickened in patients with palmar and foot hyperhidrosis than that in normal people, thus accelerating the speed of sympathetic nerve conduction, so the excitability

in patients stimulated by nervousness, excitement, stress and fever in the waking state will be enlarged, thereby increasing the sweat secreted by sweat glands; palmar and foot hyperhidrosis usually occurs during the young period or adolescence, which will continue to exist for life; it has a strong heredity with genetic probability in 30-40% (10,11).

Palmar and foot hyperhidrosis can be treated by medication and surgery; therein, medication includes topical medication, oral medication, direct current, iontophoresis and botulinum toxin injection (12). Commonly used drugs are anticholinergic agents that inhibit the action of sweat glands by competing against acetylcholine muscarinic receptors, reducing the amount of perspiration thus treating them. However, it has many side effects such as intestinal reaction, elevated intraocular pressure, dry mouth, blood pressure drop and tachycardia. Surgical treatment is usually performed by sympathectomy currently, thus inhibiting the excessive secretion of sweat glands (13). The results of this study displayed that the therapeutic effective rate in the observation group was 94.74%, which was significantly higher than 73.23% in the control group, and the difference was statistically significant ($P<0.05$). The reason is that botulinum toxin type A can inhibit acetylcholine releasing from presynaptic nerve terminals through acting on cholinergic nerve endings, thus inhibiting the secretion of sweat gland; however, long-term injection is prone to induce immune tolerance, pain of injection site and amyasthenia in patients; although they can be treated in the short-term, the disease easily relapses, which shows an uncertain long-term curative effect (14). The conduction of sympathetic nerve can be effectively blocked through burning corresponding sympathetic segment and extending to the outside, namely thoracoscopic thoracic-4 sympathetic nerve chain combined with thoracic-3 branch amputation, thus inhibiting sweat glands; once treated, it is difficult to relapse, and it has certain long-term curative effect, smaller incision of minimally invasive surgery, not obvious postoperative scar and higher satisfaction in patients (15).

Surgical trauma, combined with anesthesia and other stress reactions will inhibit the immune function and easily induces immune dysfunction, accompanied by inflammatory responses, thus leading to postoperative infection, which is not conducive to postoperative recovery of patients. CRP is an acute-phase reactive protein with high sensitivity. It can play a regulatory role by stimulating cell activation, which is commonly utilized as a marker of trauma and inflammation in the clinical practice. When the organism is damaged or has a bacterial infection, the concentration of CRP increases obviously (16-18). IL-6 is an important member of the interleukin family and plays a diverse role in the body's immune response and apoptosis (19). IL-10 can inhibit the secretion of a variety of proinflammatory cytokines, and the upregulation of its level can make the body into a highly reactive state of humoral immunity (20). As a polypeptide cytokine, TNF-α can synergistically interact with inflammatory mediators such as IL-6 and IL-10, which is an important cytokine mediating injury and infection; it is closely related to host defense function (21). The results of this study displayed that the serum levels of CRP, IL-6, IL-10 and TNF-α in patients of the two groups were higher at one week after treatment than those before treatment ($P<0.05$), and there were no significant differences between the two groups ($P>0.05$). The reason is that multi point injection therapy makes stronger sense of pain in patients, and the stress reaction can lead to abnormally increased secretion of serum cytokines; especially, the surgical treatment is more likely to cause inflammatory reaction after operation, so CRP, IL-6, IL-10 and TNF-α levels were increased compared with those before treatment. Minimally invasive surgery utilized in observation group can reduce the use of surgical instruments, plus the reduction of surgical incision length, so that the trauma is less. During the operation, the nerve was cut off by electric coagulation under direct vision using thoracoscope, and no drainage was performed after the operation, so as to reduce the stress reaction compared with routine surgery in patients and effectively decrease the occurrence of infection. Patients recovered usually at approximately one week after operation, fully demonstrating the concept of minimally invasive surgery.

After treatment for one week, IgG, IgM and IgA in patients of the two groups were obviously increased ($P<0.05$), and the differences in patients between two groups were not statistically significant ($P>0.05$). The reason is that humoral immunity in normal human will remain at a low level; the body affected by trauma will produce slight infection, while self-immune regulation occurs in the body, thus increasing the immunoglobulin IgG, IgM and IgA levels and enhancing the ability of resistance. Thoracoscopic sympathectomy has advantages of more accurate positioning, minimally invasive processing and safety, which causes less injury to normal immune function of the body, and it has little influence on the normal increase of postoperative immunoglobulin IgG, IgM and IgA levels in patients, which is conducive to the rapid recovery in patients after operation.

In summary, minimally invasive surgery adopted to treat palmar and foot hyperhidrosis has more significant effect compared with drug therapy. It causes slight postoperative inflammatory reaction and has less influence on the immune function of patients, and it can also improve the quality of life in patients. Thus, it is the ideal method for the treatment of palmar and foot hyperhidrosis, which is worthy of clinical application.

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Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contributions

WXL collected, analyzed and interpreted the patients data. YKL contributed to the conception and design of the study. HTL wrote, revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The study was approved by the Ethics Committee of Sun Yat-Sen University (Guangzhou, China). Patients provided written informed consent.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Siah TW and Hampton PJ: The effectiveness of tap water iontophoresis for palmoplantar hyperhidrosis using a Monday, Wednesday, and Friday treatment regime. Dermatol Online J 19: 14, 2013.
2. Hougaard MG and Thyssen JP: Treatment of hand eczema caused by hyperhidrosis. In: Textbook of Hand Eczema. Alikhan A, Lachapelle JM and Maibach H (eds). Springer, Berlin, Heidelberg, pp361-370, 2014.
3. Ak M, Dinçer D, Haciomeroglu B, Akarsu S, Lapsekili N and Ada S: The evaluation of primary idiopathic focal hyperhidrosis patients in terms of alexithymia. J Health Psychol 18: 704-710, 2013.
4. Yanagishita T, Tamada Y, Ohshima Y, Ito K, Akita Y and Watanabe D: Histological localization of aluminum in topical aluminum chloride treatment for palmar hyperhidrosis. J Dermatol Sci 67: 69-71, 2012.
5. Rieger R, Loureiro MP, Pedevilla S and de Oliveira RA: Endoscopic lumbar sympathectomy following thoracic sympathectomy in patients with palmoplantar hyperhidrosis. World J Surg 35: 49-53, 2011.
6. Inoue M, Yokoyama T, Ishii A, Watanabe T, Yamato T and Kumon H: The effect of hochuekkito on female stress urinary incontinence. Kampo Med 61: 853-855, 2010.
7. Inukai YS, Iwase S, Shimizu Y, Sato M, Nishimura N, Onizuka C, Kuwahara Y, Sugenoya J and Sato M: Pathogenesis of the hemifacial hyperhidrosis. J Neurol Sci 333: e712-e713, 2013.
8. Weitz G, Elam M, Born J, Fehm HL and Dodt C: Postmenopausal estrogen administration suppresses muscle sympathetic nerve activity. J Clin Endocrinol Metab 86: 344-348, 2001.
9. Nedvetsky PI, Emmerson E, Finley JK, Ettinger A, Cruz-Pacheco N, Prochazka J, Haddox CL, Northrup E, Hodges C, Mostov KE, *et al*: Parasympathetic innervation regulates tubulogenesis in the developing salivary gland. Dev Cell 30: 449-462, 2014.
10. Cerfolio RJ, De Campos JR, Bryant AS, Connery CP, Miller DL, DeCamp MM, McKenna RJ and Krasna MJ: The Society of Thoracic Surgeons expert consensus for the surgical treatment of hyperhidrosis. Ann Thorac Surg 91: 1642-1648, 2011.
11. Wolosker N, Schvartsman C, Krutman M, Campbell TP, Kauffman P, de Campos JR and Puech-Leão P: Efficacy and quality of life outcomes of oxybutynin for treating palmar hyperhidrosis in children younger than 14 years old. Pediatr Dermatol 31: 48-53, 2014.
12. Bovell DL, MacDonald A, Meyer BA, Corbett AD, MacLaren WM, Holmes SL and Harker M: The secretory clear cell of the eccrine sweat gland as the probable source of excess sweat production in hyperhidrosis. Exp Dermatol 20: 1017-1020, 2011.
13. Yuncu G, Turk F, Ozturk G and Atinkaya C: Comparison of only T3 and T3-T4 sympathectomy for axillary hyperhidrosis regarding treatment effect and compensatory sweating. Interact Cardiovasc Thorac Surg 17: 263-267, 2013.
14. Mazzocchio R and Caleo M: More than at the neuromuscular synapse: Actions of botulinum neurotoxin A in the central nervous system. Neuroscientist 21: 44-61, 2015.
15. Yang Y, Zeng L, An Z, Wang L and Hu J: Minimally invasive thoracic sympathectomy for palmar hyperhidrosis via a single unilateral incision approach by the pleura videoscope. J Laparoendosc Adv Surg Tech A 24: 328-332, 2014.
16. Nishiofuku H, Tanaka T, Marugami N, Sho M, Akahori T, Nakajima Y and Kichikawa K: Increased tumour ADC value during chemotherapy predicts improved survival in unresectable pancreatic cancer. Eur Radiol 26: 1835-1842, 2016.
17. Qin CF and Zhao FL: Long non-coding RNA TUG1 can promote proliferation and migration of pancreatic cancer via EMT pathway. Eur Rev Med Pharmacol Sci 21: 2377-2384, 2017.
18. Christensen MB, Eriksen T and Kjelgaard-Hansen M: C-reactive protein: quantitative marker of surgical trauma and post-surgical complications in dogs: a systematic review. Acta Vet Scand 57: 71, 2015.
19. Mauer J, Chaurasia B, Goldau J, Vogt MC, Ruud J, Nguyen KD, Theurich S, Hausen AC, Schmitz J, Brönneke HS, *et al*: Signaling by IL-6 promotes alternative activation of macrophages to limit endotoxemia and obesity-associated resistance to insulin. Nat Immunol 15: 423-430, 2014.
20. Zigmond E, Bernshtein B, Friedlander G, Walker CR, Yona S, Kim KW, Brenner O, Krauthgamer R, Varol C, Müller W, *et al*: Macrophage-restricted interleukin-10 receptor deficiency, but not IL-10 deficiency, causes severe spontaneous colitis. Immunity 40: 720-733, 2014.
21. DeBerge MP, Ely KH and Enelow RI: Soluble, but not transmembrane, TNF-α is required during influenza infection to limit the magnitude of immune responses and the extent of immunopathology. J Immunol 192: 5839-5851, 2014.