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Full Length Research Paper

Effect of *Astragalus mongholicus* injection liquid on the immunity function in children with congenital heart disease (CHD) after undergoing cardiopulmonary bypass surgery

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The effect of the administration of *Astragalus mongholicus* injection liquid on the immunity function in children with congenital heart disease (CHD) after undergoing cardiopulmonary bypass surgery was examined. Results showed that *A. mongholicus* injection liquid can improve the immunity function in children with CHD after undergoing cardiopulmonary bypass surgery.

Key words: *Astragalus mongholicus* injection liquid, cardiopulmonary bypass surgery, congenital heart disease (CHD), sVCAM-1.

INTRODUCTION

The traditional Chinese herb can be categorized by different functions, and *Astragalus mongholicus* (AM) belongs to the kind which can reinforce the functions of organisms. Both pharmacology and clinical practices have demonstrated that *Astragalus membranaceus* exhi-bited hepatoprotective, immunostimulating, cardiotonic and antiaging activities (Zee-Cheng, 1992; Sinclair, 1998; Cui et al., 2003). The main constituents of the root of *Astragalus* membranaceus include flavonoids, poly-saccharides, saponins, amino acids and trace elements (Shao et al., 2004). There is no recent clinical evidence to guide dosages of Astragalus products. However, typical recommendations are 2 to 6 g of the powdered root (Monograph, 2003). In traditional medicine, AM has been used for the treatment of general weakness, chronic illness and to increase overall vitality. Different peripheral effects, such as improved sensitivity to insulin (Lin et al., 2000), immune modulation, antiviral activity, anti-neoplastic activity and enhancement of cardiovascular functions have been described (Monograph, 2003). The protection of cardiovascular function might be explained in terms of protection against membrane lipid peroxidation (Chen et al., 1995; Wang et al., 1996; Toda and Shirataki, 1999).

Long-term survival in children and adults with congenital heart disease (CHD) has improved markedly with advances in medical and surgical therapies. Despite these advances, a growing number of patients with complex CHD will ultimately require heart transplantation (HT) for end-stage heart failure. CHD has been identified as a risk factor for 1-year outcome after transplantation (Lamour et al, 2009), but studies identifying specific risk factors for poor outcome after transplantation for CHD in the combined adult and pediatric population have not been performed.

In this study, we evaluated effect of *A. mongholicus* injection liquid on immunity function of children with CHD after undergoing cardiopulmonary bypass surgery.

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Table 1. Demographic comparison between groups.

Group	Number	Age (month)	Sex		CPB time (min)
			Male	Female	
A	23	98 ± 43	11	12	61 ± 22
B	21	100 ± 52	9	12	60 ± 19
C	19	99 ± 49	10	9	59 ± 18
D	20	97 ± 55	13	7	62 ± 19

METHODOLOGY

Subject and experimental design

In September 2010, Eighty-three children, ages 8 to 14 years, who were diagnosed with congenital heart disease; liver, kidney and heart failure, tumour, severe generalized infection and autoimmune diseases were excluded. Sixty-two children with congenital heart disease were randomly assigned to group B (untreated control, n = 21) or C (n = 19) and D (n = 20) (were given 2 or 4 mg/kg astragalus membranac injection liquid intravenously daily for 6 days after anesthesia induction after undergoing cardiopulmonary bypass surgery). The cardiopulmonary bypass machine used in the study was a Sarns 8000 nonpulsatile roller occlusive pump (Terumo, Belgium). The same cardiopulmonary bypass circuit set-up was used for all patients. This consists of a closed system with a soft shell reservoir and a Hilite 1000 oxygenator (Medos, Germany), which is used for flows up to 1 L/min. Patients received cold crystalloid cardioplegia (St Thomas' Solution with a K^+ concentration of 20 mmol/L) administered by the anaesthetist at a dose of 30 ml/kg after cross clamping, which then passed through the pump. All patients received one dose of cardioplegia except for four patients undergoing cavo-pulmonary shunts that did not receive any. Another 23 patients (group A) served as preoperation control. After the 7th day, central venous blood samples were taken. Plasma immunoglobulin, TNF-α, sICAM-1 and sVCAM-1 were measured.

Biochemical analysis

IgA, IgG, IgM, TNF-α, sICAM-1 and sVCAM-1 were measured using ELISA kits.

Statistical analysis

Continuous variables are presented as mean ± standard deviation, and comparisons were made by means of analysis of variance. All regression models used maximum likelihood methodology for parameter estimation. Data from both protocols were analyzed separately. All analyses were performed using statistical analysis system (SAS) statistical software version 9.1 (SAS Institute, Inc., Cary, North Carolina). Statistical significance was assumed if $P < 0.05$.

RESULTS AND DISCUSSION

A congenital heart defect (CHD) is a defect in the structure of the heart and great vessels which is present at birth. Many types of heart defects exist, most of which either obstruct blood flow in the heart or vessels near it, or cause blood to flow through the heart in an abnormal pattern (Miller et al., 2011). Other defects, such as long QT syndrome, affect the heart's rhythm. Heart defects are among the most common birth defects and are the leading cause of birth defect-related deaths. The success of cardiac surgery in childhood has produced a large population of adults with congenital heart disease. These adults present a unique challenge for the cardiology community. With more than 30 different forms of congenital heart disease, it can be difficult for adult patients to find cardiologists familiar with their particular anatomy and problems (Verheugt et al., 2008).

It is now recognised that many children with recurrent chest infections have abnormalities in their ability to produce specific antibodies to common respiratory pathogens, such as the *Streptococcus pneumoniae* or *Haemophilus influenzae* which is commonly isolated from their sputum. If an antibody deficiency is suspected, total serum levels of IgG, IgM, IgA and IgE should be measured. As the normal ranges of these proteins change during childhood, the measured values must be compared to the age-appropriate normal values, ideally from the same laboratory (Couriel, 2002).

Demographic comparison between groups is as shown in Table 1. There was no marked statistical difference in number, age, sex and cardiopulmonary bypass (CPB) time between groups. During therapy, only two patients caused slight allergic response. Other side effects in patients receiving *A. mongholicus* injection liquid were not observed.

In the present experiment, Table 2 and Figure 1 show the effect of astragalus membranac injection liquid on immunity function in children with CHD. Plasma IgA, IgG and IgM levels in children with CHD (group B) were markedly lower than those in preoperation group (A). The astragalus membranac injection liquid had considerable elevating effect on the decreased IgA, IgG and IgM levels (groups C and D) when compared with the group B.

Tumor necrosis factor (TNF or TNF-a/cachectin) is a proinflammatory cytokine that acts as a mediator of host defense against both neoplasia and infection and is principally expressed in macrophages (Beutler and Cerami, 1988; Ziegler, 1988; Old, 1987), where its secretion may be increased 10,000-fold after exposure to bacterial endotoxin lipopolysaccharide (LPS) (Beutler et al., 1986). Along with numerous beneficial roles in immune

Table 2. Effect of astragalus membranac injection liquid on IgA, IgG and IgM in children with CHD.

Group	IgA (g/L)	IgG (g/L)	IgM (g/L)
A	10.65 ± 0.96	3.86 ± 0.33	2.11 ± 0.17
B	6.06 ± 0.57[b]	1.43 ± 0.12[b]	1.08 ± 0.11[b]
C	8.57 ± 0.93[a]	2.98 ± 0.19[c]	1.79 ± 0.19[c]
D	9.96 ± 0.79[a]	3.64 ± 0.25[a]	2.12 ± 0.32[a]

[b]P < 0.01, compared with group A; [c]P < 0.05, [d]P < 0.01, compared with group B.

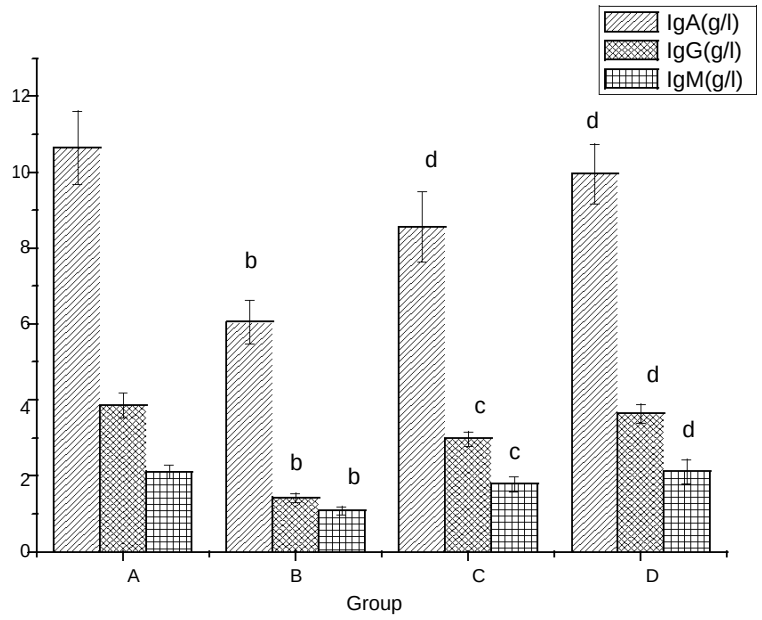

Figure 1. Effect of astragalus membranac injection liquid on IgA, IgG and IgM in children with CHD. [b]P < 0.01, compared with group A; [c]P < 0.05, [d]P < 0.01, compared with group B.

Table 3. Effect of astragalus membranac injection liquid on TNF-α in children with CHD.

Group	TNF-α
A	19.58 ± 2.43
B	11.75 ± 1.98[b]
C	15.08 ± 1.69[c]
D	18.59 ± 1.66[a]

[b]P < 0.01, compared with group A; [c]P < 0.05, [d]P < 0.01, compared with group B.

regulation, TNF has been implicated in the pathogenesis of both acute and chronic inflammatory disease (Beutler and Cerami, 1986), and therefore it is of great interest to dissect the molecular mechanisms of TNF gene expression. The observation that TNF-α is elevated in individuals with advanced heart failure (HF) prompted several high-profile clinical trials investigating whether TNF inhibitors could be used to treat HF.

Table 3 and Figure 2 show the effect of astragalus membranac injection liquid on TNF-α in children with CHD. Plasma TNF-α level in children with CHD (group B) were markedly lower than that in preoperation group (A). The astragalus membranac injection liquid had considerable elevating effect on the decreased TNF-α level (groups C and D) when compared with the group B.

Soluble cell adhesion molecules (sCAMs) are a class of cell adhesion molecule (CAM: cell surface binding proteins) that may represent important biomarkers for inflammatory processes involving activation or damage to cells, such as platelets and the endothelium (Hwang et al., 2005). In the present study, sICAM-1 in blood of children with CHD was investigated. Plasma sICAM-1 in children with CHD (group B) was found to be significantly lower than the preoperation group (A).

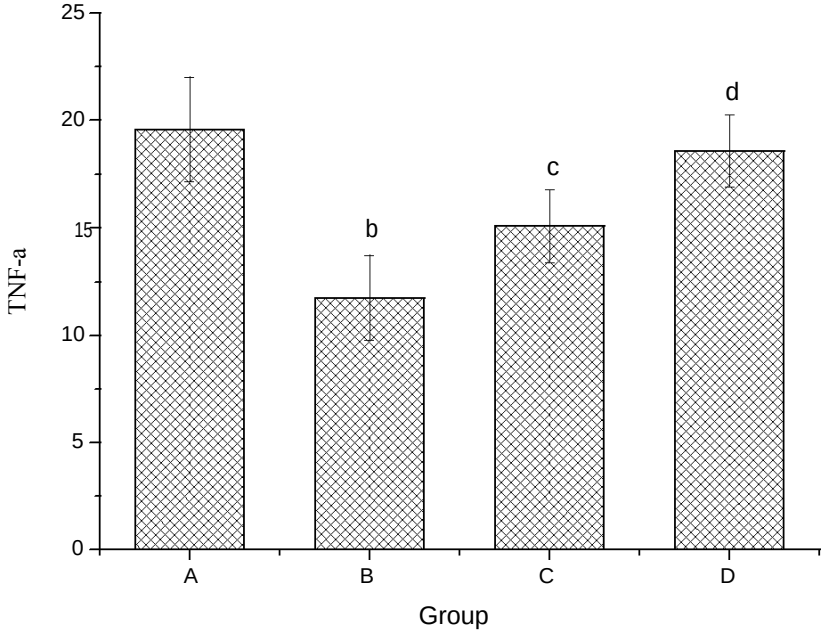

Figure 2. Effect of astragalus membranac injection liquid on TNF-α in children with CHD. $^{b}P < 0.01$, compared with group A; $^{c}P < 0.05$, $^{d}P < 0.01$, compared with group B.

Table 4. Effect of astragalus membranac injection liquid on sICAM1 in children with CHD.

Group	sICAM-1
A	395.1 ± 36.9
B	254.3 ± 27.7^{b}
C	298.4 ± 22.7^{c}
D	376.3 ± 40.5^{a}

$^{b}P < 0.01$, compared with group A; $^{c}P < 0.05$, $^{d}P < 0.01$, compared with group B.

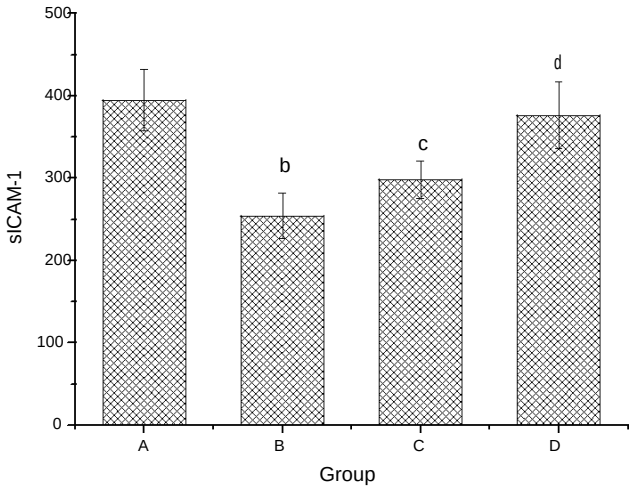

Figure 3. Effect of astragalus membranac injection liquid on sICAM-1 in children with CHD. $^{b}P < 0.01$, compared with group A; $^{c}P < 0.05$, $^{d}P < 0.01$, compared with group B.

Treatment of the astragalus membranac injection liquid after cardiopulmonary bypass surgery increased the plasma sICAM-1 in groups C and D as compared to the children with CHD (group B) (Table 4 and Figure 3).

Endothelial cells release multiple inflammatory mediators and express various adhesion molecules, such as intercellular and vascular cellular adhesion molecules (ICAM-1 and VCAM-1), P- and E-selectins (Khan and Chakrabarti, 2007). Endothelial vascular adhesion molecule-1 (VCAM-1) is a critical component of the leukocyte-endothelial adhesion cascade, and its strict temporal and spatial regulation makes it an ideal target for imaging and therapy. The counter-receptors VCAM-1 are overexpressed on the activated endothelial cell surface. They undergo shedding and their soluble forms, sVCAM-1 is detectable in the serum and is considered to be markers of endothelial cell activity or injury (Springer, 1990; Kuryliszyn-Moskal et al., 2005). Thus, endothelial cell injury and activation participate in the pathogenesis of both pulmonary hypertension (PHT) (via obliterative vasculopathy) (Seibold et al., 2001) and interstitial lung disease (ILD) (via direct and indirect roles in inducing fibroblast activation that leads ultimately to fibrosis)

Table 5. Effect of astragalus membranac injection liquid on sVCAM-1 in children with CHD.

Group	sVCAM-1
A	984.9 ± 100.8
B	684.2 ± 57.85[b]
C	842.7 ± 94.2[a]
D	965.4 ± 103.7[a]

[b]P < 0.01, compared with group A; [d]P < 0.01, compared with group B.

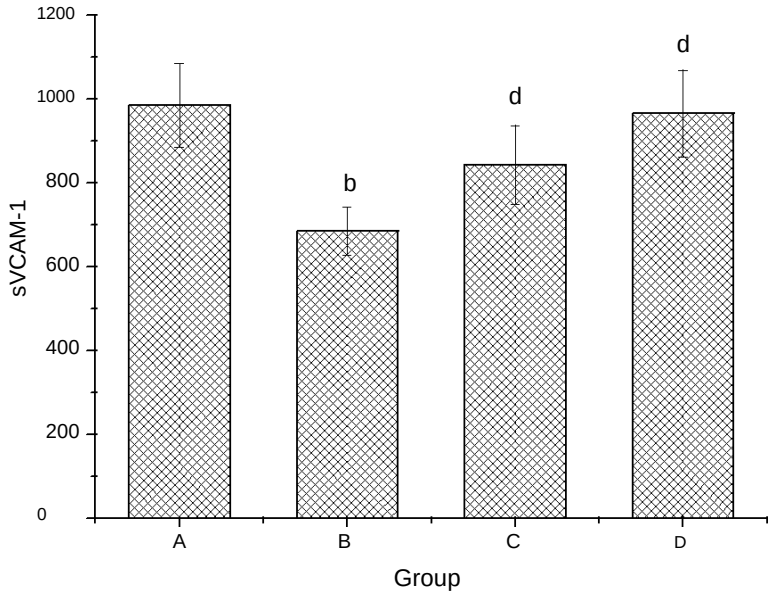

Figure 4. Effect of astragalus membranac injection liquid on sVCAM-1 in children with CHD. [b]P < 0.01, compared with group A; [d]P < 0.01, compared with group B.

(Cerinic et al., 2003).

sVCAM-1 in blood of children with CHD was investigated. Plasma sVCAM-1 in children with CHD (group B) was found to be significantly lower than the preoperation group (A). Treatment of the astragalus membranac injection liquid after cardiopulmonary bypass surgery increased the plasma sVCAM-1 in groups C and D as compared to the children with CHD (group B) (Table 5 and Figure 4).

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