Acupoint-catgut embedment combined with medication does not decrease interleukin-6 levels serum in patients with gastroesophageal reflux disease: a randomized controlled clinical trial

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ABSTRACT

BACKGROUND Gastroesophageal reflux disease (GERD) is a pathological condition caused by the reflux of stomach contents into the esophagus. GERD is a multifactorial disorder with an increase in prevalence worldwide. Interleukin-6 (IL-6) is a proinflammatory cytokine that is commonly found in the esophageal mucosa of GERD patients and associated with esophageal motor disorders. Acupoint-catgut embedment has long been known as adjunctive therapy for GERD. This study was aimed to establish the effect of acupoint-catgut embedment combined with medication on the IL-6 serum levels of patients with GERD.

METHODS This single-blind randomized controlled trial involved 40 GERD patients from the Gastroenterology Outpatient Clinic of Cipto Mangunkusumo Hospital that were randomly allocated to either catgut-embedding therapy plus medication or sham acupuncture with medication. Catgut-embedding therapy was given two times at CV12 (Zhongwan), ST36 (Zusanli), and BL21 (Weishu) every 15 days. Serum levels of IL-6 were measured by enzyme-linked immunosorbent assay as research output.

RESULTS There were no significant differences in the baseline levels of proinflammatory (IL-6) mediators between the groups. After 1-month treatment, the median levels of IL-6 were statistically insignificant decreased in catgut-embedding therapy plus medication *versus* sham acupuncture with medication (0.15 *versus* -0.16 pg/ml, respectively; $p = 0.14$).

CONCLUSIONS The results suggest that catgut-embedding therapy has not been proven to statistically influence the levels of IL-6 in patients with GERD.

KEYWORDS acupuncture therapy, GERD, interleukin-6

Gastroesophageal reflux disease (GERD) is a pathological state caused by the reflux of stomach contents into the esophagus that results in a variety of troublesome symptoms in the esophagus and extra esophagus.[1] GERD can lower health-related quality of life, and its prevalence is increasing worldwide.[1,2] The prevalence of GERD in Asia is lower than in Western countries, although some Asian countries have shown an increasing trend.[3] Data from Cipto Mangunkusumo Hospital indicate the increasing prevalence of esophagitis, from 5.7% in 1997 to 25.18% in 2002.[4] Pathological reflux is more dominant than the ability of the antireflux barrier esophagus, causing injury to the esophageal squamous epithelium tissue. Interleukin-6 (IL-6) is a proinflammatory cytokine that is commonly found in the esophageal mucosa of patients with GERD and is associated with motor disorders of the esophageal muscle.[5,6] IL-6 also naturally occurs in a soluble form, which can be found in serum.[7]

Acupuncture is now considered by medical practitioners as one of the nonpharmacological treatments of GERD. Some randomized controlled clinical trials have proven the effectiveness of acupuncture therapy for GERD, especially against the symptoms of heartburn, acid reflux, and bile salts, as well as esophageal mucosal damage.[8–10] Stimulation of acupuncture points on the peripheral nervous system causes binding between catecholamines and β2 receptor on immune cells, resulting in decreased levels of proinflammatory cytokines IL-6.[11] Acupoint-catgut embedment is one of acupuncture method that involves catgut implantation at acupoints, with advantages of using fewer acupoints, less frequent therapy, and prolonged excitatory effects.[12]

Research on the mechanisms of how acupuncture work on proinflammatory and anti-inflammatory cytokines is limited. Hence, the aim of this study was to establish the effect of acupoint-catgut embedment combined with medication on the IL-6 serum levels of patients with GERD.

METHODS

This study was a single-blind randomized clinical trial that was conducted at the Gastroenterology Clinic of Internal Medicine, Cipto Mangunkusumo Hospital, in August 2016 (Figure 1). This research was a collaboration between the Division of Gastroenterology, Department of Internal Medicine, and the Department of Medical Acupuncture. The inclusion criteria of this study were men and women aged between 18 and 59 years with a GERD questionnaire (GERDQ) score ≥8. The exclusion criteria were alarming signs such as anemia, gastrointestinal bleeding, progressive dysphagia, weight loss without definite cause, and abdominal masses, and contraindications of acupoint-catgut embedment including medical emergency, pregnancy, malignancy, blood clotting disorders, anticoagulant medication consumption, animal protein allergy history, diabetes mellitus with blood sugar levels >200 mg/dl, and previous acupoint-catgut embedment history. Calculation of the sample was based on as follows: $\alpha = 5\%$, $\beta = 20\%$, and $S = 9.82$; thus, 40 research subjects were obtained. Random allocation of samples was done using a computer-based program. Concealment technique was used to avoid procedure selection bias.

Patients who met the inclusion criteria were allocated randomly into either the catgut-embedding group plus medication or the sham acupuncture group plus medication, and then, as much as 5 cc of venous blood sample was drawn. On day 1, acupoint-catgut embedment at CV12 (Zhongwan), ST36 (Zusanli), and BL21 (Weishu) was done (Figure 2). Then, the same procedure was repeated at these points on the 15th

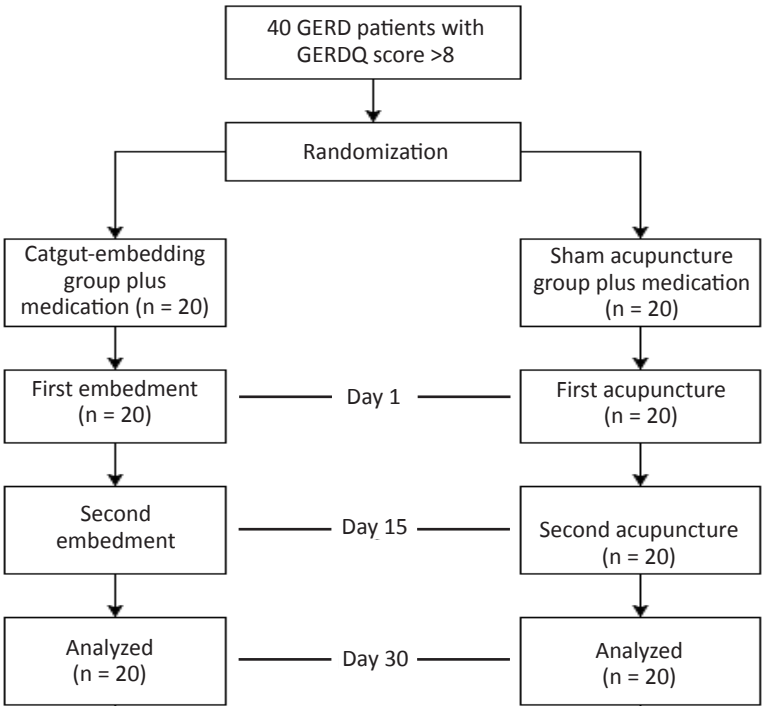

Figure 1. Diagram of subject recruitment. GERD=gastroesophageal reflux disease; GERDQ=GERD questionnaire; IL-6=interleukin-6

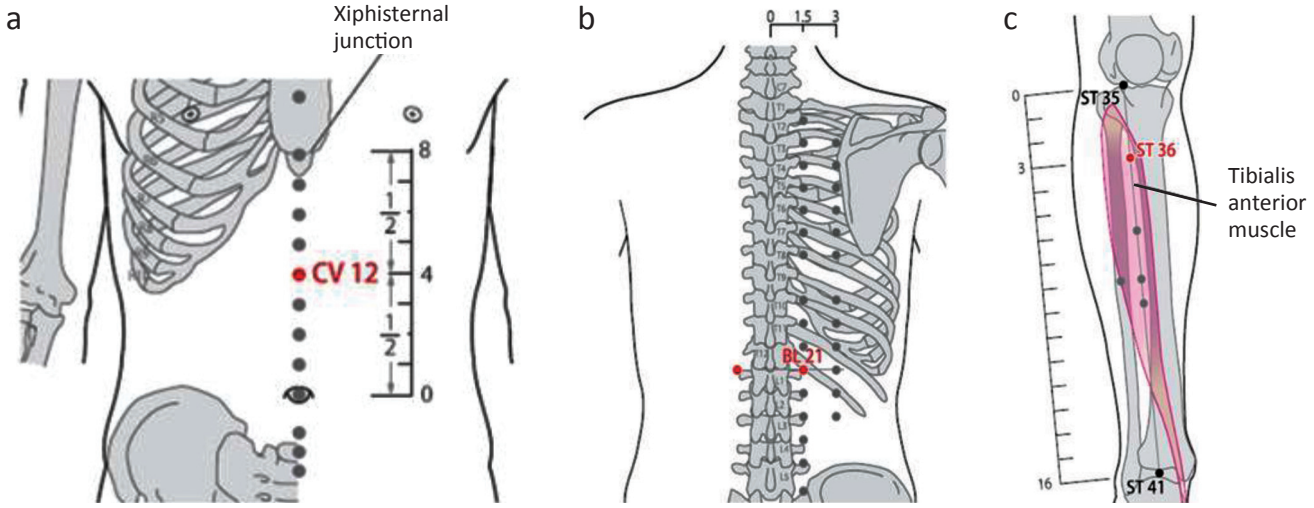

Figure 2. Acupuncture points. (a) CV12 (Zhongwan); (b) BL21 (Weishu); (c) ST36 (Zusanli)

day. The process in the sham acupuncture group is almost the same as the catgut-embedding group, only that the latter touches the skin surface at a predetermined point. On the 30th day, as much as 5 cc of venous blood sample was drawn again. IL-6 was examined at the Laboratory of Research and Esoteric Prodia using the Human IL-6 Quantikine® HS enzyme-linked immunosorbent assay (ELISA) kit (R&D Systems Inc., Minneapolis, USA), which employs the quantitative sandwich enzyme immunoassay technique. This is a special kit intended for this research.

Data were analyzed using the SPSS software, version 23 (IBM). The Mann–Whitney *U* test was performed for the inter-group analysis and Wilcoxon signed-rank test for intra-group analysis.

This research has been approved by the Health Research Ethics Committee of the Faculty of Medicine, Cipto Mangunkusumo Hospital, through letter no. 688/UN2.F1/ETHICS/2016. The subjects involved in the study have agreed to participate by signing an informed consent of confidentiality and voluntary noncoercion.

RESULTS

This study was conducted on 40 patients with GERD who met the inclusion and exclusion criteria. The characteristics of the research subjects are listed in Table 1.

Comparison of the median difference in the levels of IL-6 in the catgut-embedding therapy and sham acupuncture groups was not statistically significant

Table 1. Characteristics of the subjects

Characteristics	Acupoint-catgut embedment group, n (%)	Sham group, n (%)
Age (years), median (min–max)	47 (20–58)	41.5 (20–57)
Sex		
Male	2 (10)	2 (10)
Female	18 (90)	18 (90)
Occupation		
Housewives	9 (45)	8 (40)
College student	1 (5)	1 (5)
Civil employees	0 (0)	4 (20)
Professional	1 (5)	3 (15)
Private employees	8 (40)	3 (15)
Entrepreneur	0 (0)	1 (5)
Retirement	1 (5)	0 (0)
Drugs usage		
PPI	11 (55)	11 (55)
H2 blocker	1 (5)	1 (5)
Antacid	6 (30)	4 (20)
Not taking any drugs	2 (10)	4 (20)
GERDQ score (log 10), mean (95% CI)	9.8 (9.1–10.5)	10.4 (9.5–11.3)
Early levels IL-6, median (min–max)	3.3 (1.1–14.7)	2.1 (0.72–7.2)

PPI=proton-pump inhibitor; H2 blocker=histamine 2 blocker; GERDQ=gastroesophageal reflux disease questionnaire; CI=confidence interval; IL-6=interleukin-6

Table 2. Comparison of median difference in the levels of IL-6

IL-6 level	Acupoint-catgut embedment group, median (min–max)	Sham group, median (min–max)	*p**
Pre-intervention	3.3 (1.1–14.7)	2.1 (0.72–7.2)	0.38
Post-intervention	2.9 (0.88–16.3)	1.7 (1.0–7.3)	0.06
Δ IL-6	0.15 (-4.2–5.7)	-0.16 (-4.4–1.6)	0.14

IL-6=interleukin-6
*Mann–Whitney U test

(p = 0.14; Table 2). There was no difference of IL-6 between pre- and post-catgut-embedding therapy (p = 0.59).

DISCUSSION

This was the first study in Indonesia that uses acupoint-catgut embedment in GERD patients to evaluate the changes of IL-6 serum levels. The result showed that there was a decrease in the levels of IL-6 in patients with GERD after catgut-embedding therapy plus medication, but the decline is small and it did not show significant differences. Median changes of IL-6 were 0.15 in the catgut-embedding therapy group and -0.16 in the sham acupuncture group. There was no difference of IL-6 in the catgut-embedding therapy and sham acupuncture (p = 0.14).

Study on acupuncture in GERD is very limited. However, previous studies, including Dickman et al,[8] Zhang et al,[9] Zhang et al,[13] and Baginda et al,[14] have shown that acupuncture therapy was better at lowering symptom scores and improving quality of life in patients with GERD.[14]

The medications used for comparison in this study were mostly PPI, which is the standard therapy for patients with GERD. PPIs have anti-inflammatory effects by inhibiting the production of proinflammatory cytokines. Giving lansoprazole can reduce proinflammatory cytokines including IL-6, IL-8, and tumor necrosis factor-α (TNF-α). The mechanism of how PPI can reduce the production of proinflammatory cytokines in the epithelial and endothelial cells is still not clear.[15] A study by Hashioka et al[16] about the anti-inflammatory effects of PPIs (lansoprazole and omeprazole) in the microglial cells has shown that both PPIs significantly reduced the levels of TNF-α and IL-6. This suggests that PPI has anti-inflammatory effects and can lower neurotoxicity in human microglial cells.[16]

In this study, the IL-6 level showed a reduction after the intervention in both the treatment and control groups. However, these results were statistically insignificant. This can be due to participants in each group were still taking PPI during research so the inflammatory mediators can decrease despite the intervention of acupoint-catgut embedment therapy.

IL-6 is a pleiotropic cytokine that has broad biological activity in the regulation of the immune system, hematopoiesis, inflammation, and oncogenesis.[17] Various diseases caused by chronic inflammation such as rheumatoid arthritis, systemic lupus erythematosus, ankylosing spondylitis, psoriasis, colitis, and obesity can contribute to increased levels of IL-6. The exclusion criteria in this study did not remove other inflammatory diseases, as this may cause an insignificant decrease in IL-6 levels. Therefore, we had to be strict on selecting the subjects to obtain better research results.

IL-6, although largely a proinflammatory cytokine, can also act as anti-inflammatory cytokines.[7,17–19] In this study, the decreased levels of IL-6 were not significant. This might happen because of synergism between the anti-inflammatory effects of acupuncture and the role of IL-6 as anti-inflammatory cytokines instead of proinflammatory cytokines, which were considered as the pathophysiology of GERD.

Various studies suggest that stimulating acupuncture points on the peripheral adrenal axis could activate neuroendocrine, which could result in increased catecholamines. The bond between catecholamines and β2 adrenergic receptors on immune cells triggers a decline in the levels of proinflammatory cytokines IL-6.[19] These results have been inconsistent with the theory of acupoint-catgut embedment therapy as there are insignificantly reduced levels of IL-6.

The limitations of this study include the consumption and lack of intake schedule of PPI that had an anti-inflammatory effect on the study subjects and the absence of other chronic disease exclusion in the study subjects that can reduce IL-6 levels without acupuncture, even though this has been anticipated by doing randomization. However, if the exclusion criteria are very strict, then it will be difficult to extrapolate the research results into the community. In addition, a short study time of only 1 month and catgut-embedding therapy done only two times is not standard therapy. There is also no other outcome assessment such as decreased drug requirements, clinical assessment with GERDQ, anatomical assessment, and quality of life evaluation.

In conclusion, this study suggests that catgut-embedding therapy has not been statistically proven to influence the levels of IL-6 in patients with GERD ($p > 0.05$). Catgut-embedding therapy can still be used as adjunctive therapy in addition to regular PPI therapy as it provides some reduction in IL-6 levels.

Conflict of Interest

The authors affirm no conflict of interest in this study.

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