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Letter to the Editor

Evaluation of therapeutic effect and cytokine change during transplacental Digoxin treatment for fetal heart failure associated with fetal tachycardia, a case–control study

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Persistent fetal tachycardia may lead to congestive heart failure, hydrops fetalis, and even fetal/neonatal death. Previous studies revealed that Digoxin represents one of the first-line agents for fetal tachycardia and heart failure with the advantages of high efficiency of placental transportation and low retention [1–4]. Recently, with multiple evaluation systems, we examined the efficacy of transplacental Digoxin therapy in our hospital with a focus on amelioration of the fetal conditions before and after treatment [5]. However, it is still controversial whether Digoxin can improve the long-term pregnancy outcome.

In the current study, we conducted a case–control study to compare the long-term pregnancy outcome between Digoxin and control groups. We found that while the majority of Digoxin group had normal healthy neonates, the majority of control group ended up early termination. Furthermore, to determine the response of mother to the Digoxin treatment, we examined levels of several parturition-initiating cytokines between control and Digoxin-treated groups.

From May 2008 to Dec. 2010, a total of 14 gravidas with fetal tachycardia and hydrops were recruited into the current study. Signed consent form was obtained from all of subjects. Among them, 8 cases were atrial flutter (AF) ($n = 4$ in treated group and 4 in control group); 6 cases of supraventricular tachycardia (SVT, $n = 2$ in treated group and 4 in control group) (Supplementary Table 1). All of the gravidas were healthy without signs or history of the following pathological conditions: cardiac arrhythmia, rheumatic disorder, viral infection, pregnancy-induced hypertension, placental aging, radiation/drug exposure, and family history of cardiac arrhythmia and congenital heart disease. In addition, a total of 52 healthy gravidas without abnormal fetal conditions were recruited and divided into two groups. Those with the sign of parturition were included in Onset group ($n = 22$) and those without parturition sign were included in Quiescence group ($n = 30$).

All patients were subjected to echocardiographic examination (GE Vivid 7-color ultrasound, GE, USA). Cardiovascular profile score (CVPS) was calculated with the method by Huhta et al. [6,7]. With written informed consent, transplacental Digoxin therapy was started with an initial dosage of 0.25 mg bid and adjusted according to the serum concentration, as well as fetal condition indicated by CVPS score. Over the treatment course, Digoxin level in maternal serum was maintained in the range of 0.84–1.43 ng/ml. Fetal CVPS and maternal serum Digoxin levels were assessed every 5–7 days. This study was approved by the Ethics Committee of West China Second University Hospital of Sichuan University.

Maternal serum samples of recruited subjects were used to measure concentration of cortisol (Cort), tumor necrosis factor-alpha (TNF-α), Interleukin-1beta (IL-1β) and Interleukin-6 (IL-6) using ELISA kits purchased from R&D systems (Shanghai, China) and Multifunctional microplate reader (Infinite 200, TECAN. Shanghai, China). One-way ANOVA (SPSS program, ver. 18.0, USA) was used for the comparisons

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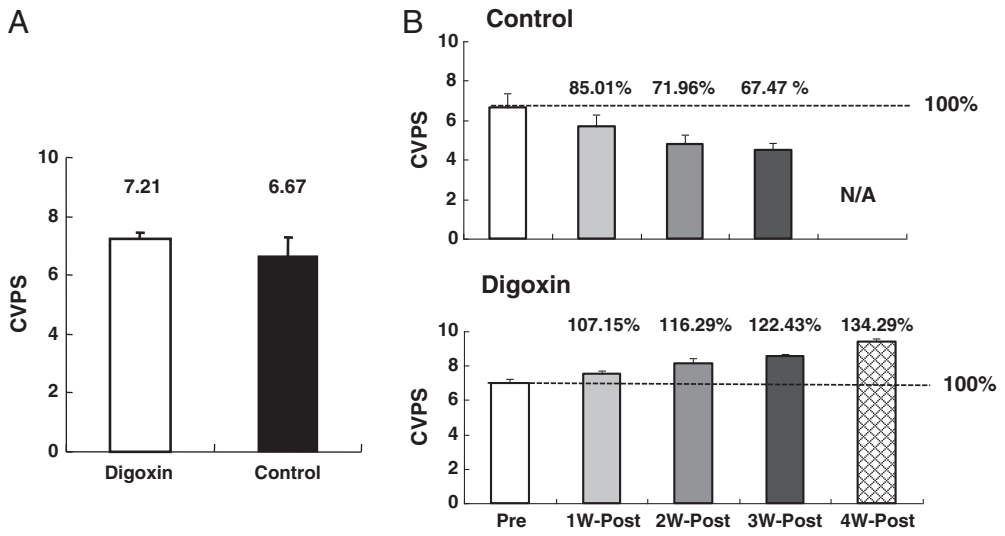

Fig. 1. Digoxin treatment improved fetal heart function and pregnancy outcome. The basal line (A) and change of CVPS in control (B) and Digoxin (C) groups (Pre = before the treatment; W-post = week post treatment initiation).

of multiple groups and student's *t*-test for two-group comparisons. The differences were considered significant when $p < 0.05$.

As shown in Fig. 1, at the time of study initiation, the control and Digoxin groups showed similar basal line of fetal CVPS. During 4-week observation period, control group showed a continuous decrease of fetal CVPS, which dropped to 67.47% of baseline at 3 week post study initiation. Ten out of 12 (83.3%) control cases had a termination outcome at 4 week post initiation of observation (Supplementary Table 1). In contrast, Digoxin group showed a continuous increase of fetal CVPS, which increased to 134.29% of baseline (approaching 10 point of the CVPS score) at 4 week post initiation. Eight out of 10 (80%) cases of AF and STV with Digoxin treatment ended up healthy neonates. These data indicated that Digoxin treatment improved fetal condition as well as the pregnancy outcomes in patients with fetal AF or STV.

It has been reported that cortisol (CORT) and inflammatory cytokines, such as IL-1β, IL-6 and TNF-α play roles in the initiation of delivery, because they may promote the production of prostaglandin E2 (PGE2), which in turn causes the contraction of uterine [8,9]. As

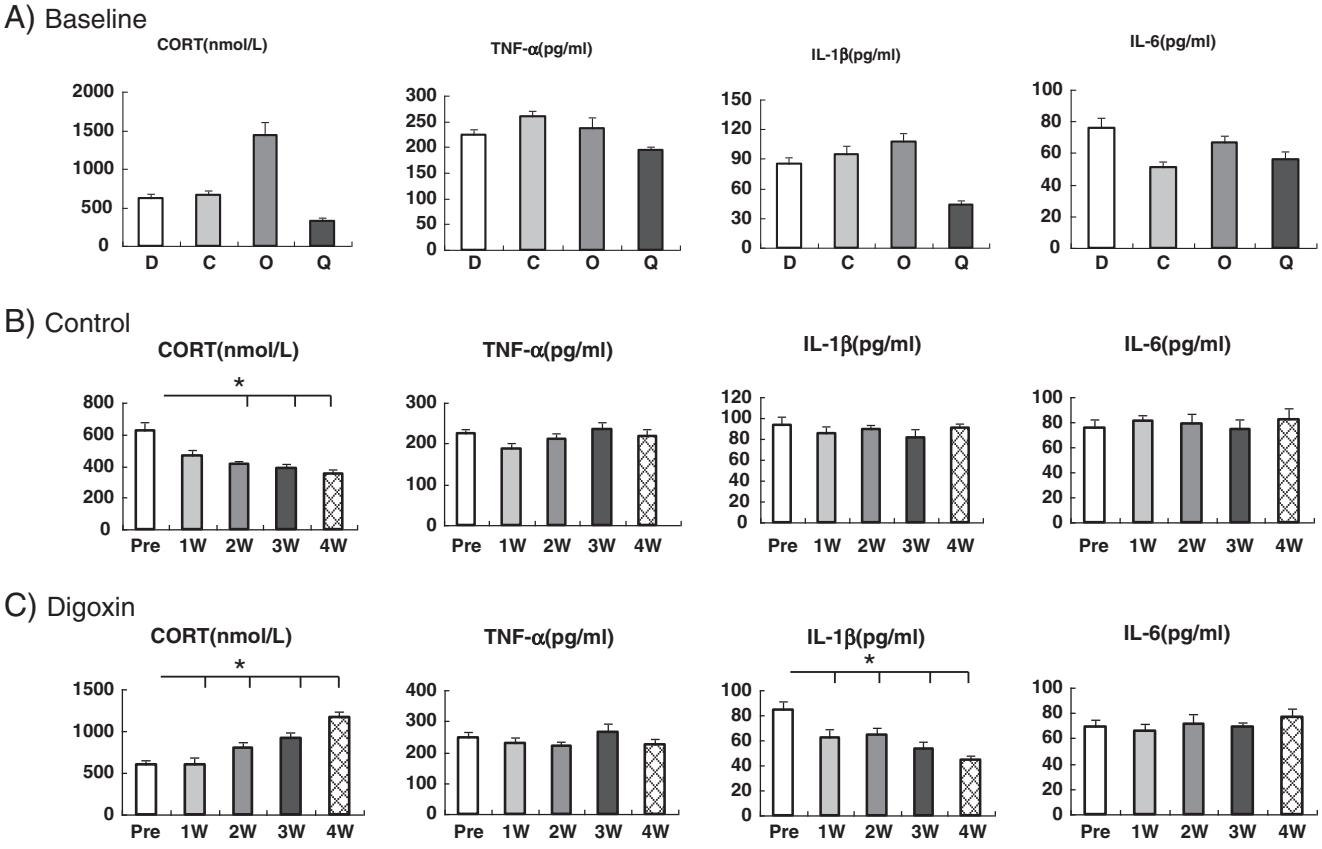

Fig. 2. Digoxin treatment decreased cortisol and IL-1β levels in maternal serum. Maternal serum concentrations of Cortisol, TNF-α, IL-1β and IL-6 were measured with ELISA (A, D = Digoxin; C = Control; O = Onset; Q = Quiescence; Pre = before the treatment; W = week post treatment initiation; *, $p < 0.05$).

expected, normal healthy gravidas showed lower levels of these cytokines in quiescence status (group Q) than in onset status (group O) (Fig. 2A). However, while the baselines of these cytokines were similar in Digoxin and control groups (2A), the two groups of patient show opposite trend of cortisol level changes: continuous increase in control group (2B) and decrease in Digoxin group (2C). TNF-α and IL-6 level did not alter by Digoxin treatment, nor did change over the time. IL-1β levels did not significantly change over the time in observational group but significantly decrease in Digoxin group.

Transplacental Digoxin treatment improved pregnancy outcome and fetal condition in patients with fetal heart failure associated with fetal tachycardia. Digoxin's beneficial effect on pregnancy outcome is achieved, at least partially, via regulating the level of parturition-initiating factors.

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