Comparison of Low Molecular Weight Heparin Used alone or Combined with Aspirin in the Treatment of Fetal Growth Restriction

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ABSTRACT

The objective of the study was to compare the efficacy of low-molecular weight heparin (LMWH) alone and use in the combination with aspirin in the treatment of fetal growth restriction (FGR) patients. Ninety-six FGR patients were divided into the LMWH group (n=48) and the combined group (n=48), according to the different treatments. This research showed after treatment, values of PI, RI and S/D, serum IL-6 and TNF-α in the combined group were lower than those in the LMWH group (all p <0.001). The frequency of pregnancy complications and adverse neonatal outcomes in the combined group were 2 (4.2%) lower than the LMWH group (p=0.045, 0.025). Combination of LMWH with aspirin in FGR patients effectively reduced levels of IL-6 and TNF-α within the mother, improved fetal developmental parameters, and reduced the frequency of pregnancy complications and adverse neonatal outcomes compared with LMWH treatment alone.

Key Words: *Fetal growth restriction (FGR), Low-molecular weight heparin (LMWH), Aspirin, Pregnancy, Newborn.*

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Fetal growth restriction (FGR) is one of the serious complications in obstetrics. During FGR, significantly reduced blood supply to the uteroplacenta, together with the inflammatory response, exacerbates villi ischemia and hypoxia. As a result, a compromised supply of the nutrients and oxygen to the fetus *in utero* can ultimately affect fetal growth and development as well as maternal and infant outcomes.[1] It has been found that fetuses with FGR are susceptible to intrauterine distress, neonatal asphyxia, meconium aspiration syndrome, preterm delivery, and intrauterine death during the perinatal period.[2,3] Therefore, it is imperative to provide timely effective treatment to the pregnant women with FGR.

Low molecular weight heparin (LMWH) enhances antithrombin III activity, raises blood viscosity, reduces vascular resistance, and improves placental blood supply.[4] It has also been shown that LMWH has anti-inflammatory and microcirculation-regulating effects, which may promote fetal development.[5] LMWH combined with aspirin may exert a synergistic effect of antithrombosis, improve tissue microcirculation, improve placental perfusion, and facilitate the delivery of adequate oxygen and nutrients to the fetus.[6] The aim of this study was to compare the efficacy of LMWH alone and use in combination with aspirin in the treatment of FGR patients.

This retrospective study was approved by the Hospital Ethics Committee of Xinchang people's Hospital, China. Ninety-six FGR patients, who presented to the Xinchang people's Hospital, China, from January 2020 to December 2021, were included. Inclusion criteria were that the patients met diagnostic criteria of FRG; age >20 years; singleton pregnancy; and signed the informed consent. Exclusion criteria were: FGR due te congenital anomalies or chromosomal abnormalities; twin or multiple pregnancies; pregnancy complications such as placenta praevia, amniotic fluid abnormalities, placental abruption, gestational hypertension;kic abnormalities; abnormal fetal development; intolerance to the LMWH or aspirin.

Ninety-six patients were divided into LMWH group (n=48) and combined group (n=48), according to different treatments. Combined group was treated with LMWH in combination with aspirin, *i.e.* oral aspirin at 50 mg/d for 4 weeks based on LMWH group.

Ultrasound Doppler was used to detect and compare the umbilical artery flow parameters before and after the treatment in the two groups, including the values of PI, RI, and S/D calculated

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from the blood flow velocities. Levels of serum IL-6 and TNFα of the pregnant women were determined by ELASA before and after the treatment.

The frequency of placental abruption, oligohydramnios, fetal distress, and other pregnancy complications was compared between the two groups. The incidence of adverse neonatal outcomes (including preterm birth, very low birth weight babies, and neonatal asphyxia) was compared between the two groups.

Statistical analyses were conducted using SPSS 25. Shapiro-Wilk test was used for testing the data normality. The measurement data that fit normal distribution were expressed by the mean±SD. Enumeration data were expressed by n (%). The difference between measurement data was analysed with an independent sample t-test. Enumeration data was compared with a chi-squared test. $p < 0.05$ was interpreted as significant.

In LMWH group, patients were aged 28.75±5.46 years (20-40). In the combined group, patients were aged 28.73±5.45 years (20-40). There was no significant difference in age between the two group (p=0.985).

Table I: Umbilical artery blood flow parameters.

Parameter	LMWH group (n=48)	Combined group (n=48)	p
PI before treatment	1.40±0.12	1.41±0.12	0.713*
PI after treatment	0.92±0.08	0.80±0.07	<0.001*
RI before treatment	1.01±0.09	1.02±0.10	0.741*
RI after treatment	0.69±0.06	0.60±0.05	<0.001*
S/D before treatment	3.20±0.28	3.22±0.29	0.678*
S/D after treatment	2.65±0.23	2.30±0.20	<0.001*
Serum IL-6 before treatment (ng/mL)	69.22±6.10	69.64±6.14	0.737*
Serum IL-6 after treatment (ng/mL)	65.43±5.66	57.71±5.09	<0.001*
Serum TNF-α before treatment (ng/L)	44.40±3.91	44.50±3.92	0.900*
Serum TNF-α after treatment (ng/L)	38.15±3.36	35.68±3.14	<0.001*

**Independent sample t-test was used; PI: Pulsatility index; RI□Resistance index; S/D: Systolic/diastolic ratio; IL-6: interleukin-6; TNF-α: tumor necrosis factor-α.*

Before the treatment, PI, RI, and S/D between the two groups were not significantly different (p=0.713, 0.741, and 0.678, respectively); after treatment, PI, RI, and S/D in the combined group were lower than those in LMWH group ($p < 0.001$, Table I).

Before treatment, serum IL-6 and TNFα between the two groups were not significantly different (p=0.737, and 0.900 respectively, Table I); after treatment, the above indicators in the combined group were lower than those in the LMWH group (both $p < 0.001$, Table I).

Incidence of pregnancy complications in the LMWH group was 8 (16.7%), including 3 (6.3%) cases of placental abruption, 4 (8.3%) cases of oligohydramnios, and 1 (2.1%) case of fetal distress. The incidence of pregnancy complications in the combined group was 2 (4.2%), including 2 (4.2%) cases of oligohydramnios. The incidence of pregnancy complications in the combined group was lower than the LMWH group (p=0.045).

The frequency of adverse neonatal outcomes in the LMWH group was 9 (18.8%), including 3 (6.3%) cases of preterm infants, 5 (10.4%) cases of very low birth weight infants, and 1 (2.1%) case of neonatal asphyxia. The incidence of adverse neonatal outcomes in the combined group was 2 (4.2%), including 1 (2.1%) case of preterm infant and 1 (2.1%) case of very low birth weight infant. The incidence of adverse neonatal outcomes was lower in the combined group than LMWH group (p=0.025).

The results of this study showed that the combination of LMWH with aspirin in FGR patients effectively reduced levels of inflammatory factors IL-6 and TNFα within the mother, improved fetal developmental parameters, and reduced the incidence of pregnancy complications and adverse neonatal outcomes compared to the LMWH treatment alone. Nevertheless, a larger sample size is needed to evaluate the efficacy of LMWH combined with aspirin in treating FGR, given the relatively small sample size of this study.

ETHICAL APPROVAL:

The study was conducted with the approval of the Hospital Ethics Committee.

COMPETING INTEREST:

The authors declared no competing interest.

AUTHORS' CONTRIBUTION:

SH: Drafted the work, analysed, and interpreted the data.
LL: Drafted the work and revised it critically.
SH: Revised it critically and approved to be published.
All the authors have approved the final version of the manuscript to be published.

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