Trihydroxyethylrutosides in the Treatment of Hemorrhoids of Pregnancy : A Double-Blind Placebo-Controlled Trial

VITAYA TITAPANT, M.D.*, BANJOB INDRASUKHSRI, M.D.**,
VIRIYA LEKPRASERT, M.D.*, WIROON BOONNUCH, M.D.**

Abstract

The safety and efficacy of Trihydroxyethylrutosides (HR) in the treatment of 53 patients with 1st-2nd degree hemorrhoids of pregnancy (16th-34th week) was investigated in a double-blind randomised, placebo controlled trial. The dosage of Trihydroxyethylrutosides was 1 tablet of 300 milligrams twice daily for the first 2 weeks. If the treatment was successful, the treatment was stopped. If the clinical signs or symptoms still persisted, the treatment was continued for another two weeks using the same dosage and re-evaluated at the end of the fourth week after initial treatment. The parameters for efficacy were symptoms (pain, bleeding, exudation and pruritus) and the objective signs on proctoscopy (bleeding, inflammation and dilatation of the hemorrhoidal venous plexus).

The study revealed improvement of symptoms in the study group which was better than in the control group after 2 weeks of treatment but the clinical signs were not different. After a further 2 weeks of treatment, the result showed improvement of both clinical signs and symptoms in this study. Only one mild transient side effect was reported in the HR group and there were no drug-related problems in the pregnancies, delivery or the babies.

Key word : Hemorrhoids, Pregnancy, Trihydroxyethylrutosides

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It has been estimated that about one third of pregnant women complain spontaneously of hemorrhoids and in around 60 per cent, abnormal dilatation of the hemorrhoidal venous plexus can be observed on proctoscopy(1). It has also been found that 46 per cent of the pregnant women who attended the antenatal clinic had hemorrhoids that needed treatment(2). At present, in Siriraj Hospital,

* Department of Obstetrics and Gynecology,
** Department of Surgery, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand.

the problem of hemorrhoids of pregnancy has not been of concern by both the obstetricians and the patients themselves. It could be that many patients attend the clinic every day and obstetricians do not have enough time for this problem. The pregnant women themselves, usually do not tell the obstetricians even if they have symptoms of this problem. Perhaps they are too shy or because they only have minor symptoms. So this problem still lacks appropriate care.

The aetiological factors generally considered to be related to the high incidence of hemorrhoids of pregnancy are as follows:

- hormonal factors resulting in an increase of venous smooth muscle tone;
- increased blood volume with elevated hydrostatic pressure;
- the enlarged uterine mass impeding venous return from the hemorrhoidal plexus;
- the high incidence of constipation during pregnancy.

The usual symptoms of hemorrhoids of pregnancy are pain, bleeding, exudation (oozing discharge) and pruritus. Bleeding may be the cause of anemia in pregnancy from iron deficiency. Only 15 millilitres of blood loss, 7 milligrams of iron, which is comparable to daily requirement[3], will be lost. If the bleeding persists for a long time, the patient may need surgical intervention.

The treatment of hemorrhoids depends on the severity of the disease. The usual treatments of hemorrhoidectomy, sclerosing, ligation, dilatation of anal sphincter, cryotherapy are not suitable for a pregnant woman. In addition, the hemorrhoids will often improve spontaneously after delivery so that the main objective during pregnancy is usually to provide symptomatic relief. For this reason, topical treatment with various forms of creams or suppositories are very often used.

Previous publications have shown good results with the oral administration of Trihydroxyethylrutoside (HR) in the treatment of hemorrhoids [1,4]. The principle pharmacological effect of HR is a reduction of microvascular permeability and oedema, shown in various animal models[8,9,10] and in patients with chronic venous insufficiency[4, 5,6]. Its safety and efficacy in pregnancy, usually for the treatment of the symptoms related to varicosis, has been well established[1,11,12]. We decided to undertake a double-blind, randomised, placebo controlled trial with HR in women with hemorrhoids of pregnancy.

PATIENTS AND METHOD

Sixty patients in the Department of Obstetrics and Gynecology and the Department of Surgery, Faculty of Medicine Siriraj Hospital, Mahidol University were recruited to the trial on the basis of the following inclusion criteria:

- Symptoms and signs (pain, bleeding, pruritus and mass) which started during this pregnancy.
- First or second degree hemorrhoids:

First degree : Hemorrhoids which bleed but do not protrude through the anus.

Second degree : Hemorrhoids which protrude on defaecation and reduce spontaneously.

- Between 16^{th} and 34^{th} week of pregnancy.
- Singleton pregnancy with no medical or obstetric complications.
- No other treatment except for vitamins.
- Agreement to give voluntary written informed consent.

Patients with third degree hemorrhoids (protruding that need digital replacement) and fourth degree hemorrhoids (continuously protruding) were excluded. At the first visit, a full history, including past and present obstetric history was taken from the patients and a proctoscopy was performed by an anorectal surgeon to establish the degree of severity and the appearance of the hemorrhoid.

The objective signs were classified for severity as follows:

1) Mild:

If only one of 3 objective signs (bleeding, inflammation, vein dilatation) was present.

2) Moderate :

If two of these three signs were present.

3) Severe :

If all three signs were present.

The subjective classification of severity was also established on the basis of the symptoms as follows :

1) Mild :

If only one of 4 symptoms (pain, bleeding, exudation, pruritus) was present.

2) Moderate :

If two of these symptoms were present.

3) Severe :

If more than two symptoms were present.

An examination by ultrasonography was also performed to exclude any foetal abnormalities on entry to the trial. After that, the patients were randomly allocated to two groups. Thirty-one patients in the study group received oral Trihydroxyethylrutosides 600 milligrams daily in equally divided doses for 2 weeks while the control group consisted of twenty-nine patients who received a corresponding oral placebo of identical appearance. They were given a pack with 28 tablets of the drug (or placebo) at the first visit. The patients were seen again after 2 weeks (the end of the first episode of treatment). At this visit the symptoms were re-assessed by the same scoring basis. The occurrence of any side effects were noted and proctoscopy was repeated to re-evaluate the objective signs.

At the end of the treatment the patient's overall opinion was obtained on the basis of:

1) Unchanged:
No improvement in symptoms.

2) Improved:
One of the initial symptoms had disappeared.

3) Much improved:
Two or three initial symptoms had disappeared.

4) Cured:
All symptoms had disappeared

The doctor also gave an overall judgement of the treatment:

1) Ineffective:
No improvement of symptoms or objective signs.

2) Effective:
Clear symptomatic improvement but not of objective signs.

3) Very effective:
Clear improvement in both symptoms and objective signs.

If any of the patients had no signs and symptoms, the treatment was stopped. If they still had any signs or symptoms, they were given a second pack of 28 tablets of the drug (or placebo).

The patients were seen again after another 2 weeks of treatment for reassessment.

The patients were also seen for the fourth time after delivery to establish the status of the baby. Methods of delivery, birth weight, Apgar scores and any foetal abnormalities were recorded.

Statistics

For comparison of the patients' initial characteristics between the two treatment groups (numerical values), the Student *t*-test was used. For comparison of the efficacy of the two treatment regimens (i.e. patients' own overall opinion and the doctors' overall judgement of efficacy), the chi-square test was used. In certain cases where numbers were too small (less than 5 patients), we used the Fisher's exact test. For comparison of methods of delivery, birth weight and Apgar scores, we used Mann-Whitney and Levene's test respectively.

RESULTS

Of the sixty patients who entered the trial, three in the study group and four in the control group dropped out of their own volition and were lost to follow-up.

Patient Characteristics

The initial characteristics of the remaining 53 patients who completed the trial and were evaluated (27 HR/26 placebo) are shown in Table 1.

This shows that there were no significant differences ($P > 0.05$) between the two groups re-

Table 1. Patients' initial characteristics.

Characteristics	HR (n = 27)	Placebo (n = 26)	P-value
Age (years)	25.3 ± 4.9	23.5 ± 4.3	0.14
Gravida	1.6 ± 0.8	1.6 ± 0.9	0.66
Parity	0.4 ± 0.7	0.4 ± 0.5	0.09
Gestational age (weeks)	20.7 ± 6.1	20.8 ± 5.6	0.96

Table 2. Patients' overall opinion of treatment at the end of 2 weeks.

Patients' opinion	HR (n = 27)		Placebo (n = 26)		P-value
	n	%	n	%	
Unchanged	6	22.0	13	50.0	
Improved	1	3.7	3	11.5	
Much improved	6	22.2	1	3.9	0.04
Cured	14	51.9	9	34.6	
Total	27	100.0	26	100.0	

Table 3. Patients' overall opinion of treatment at the end of 4 weeks.

Patients' opinion	HR (n = 27)		Placebo (n = 26)		P-value
	n	%	n	%	
Unchanged	0	0	11	42.3	
Improved	1	3.7	0	0	
Much improved	2	7.4	5	19.2	0.003
Cured	24	88.9	10	38.5	
Total	27	100.0	26	100.0	

Table 4. Doctors' overall evaluation of the efficacy of treatment after 2 weeks.

Doctors' evaluation	HR (n = 27)		Placebo (n = 26)		P-value
	n	%	n	%	
Ineffective	4	14.8	8	30.8	
Effective	18	66.7	13	50.8	0.35
Very effective	5	18.5	5	19.2	
Total	27	100.0	26	100.0	

Table 5. Doctors' overall evaluation of the efficacy of treatment after 4 weeks.

Doctors' evaluation	HR (n = 27)		Placebo (n = 26)		P-value
	n	%	n	%	
Ineffective	0	0	8	30.8	
Effective	20	74.1	16	61.5	0.004
Very effective	7	25.9	2	7.7	
Total	27	100.0	26	100.0	

garding age, gravidity, parity and the duration of pregnancy on entering the trial.

Efficacy

The patients' overall opinion on the treatments as related to their symptoms is shown in Table 2 and 3.

This shows that there were significant differences ($P < 0.05$) in the patients' overall opinion of the treatment at the end of 2 and 4 weeks between the two groups.

Doctors' overall evaluation of the efficacy of treatment is shown in Table 4 and 5.

This shows that there were significant differences ($P < 0.05$) in the efficacy of treatment after 4 weeks.

Side effects

Only one patient reported nausea which happened after 2 weeks of treatment and diminished spontaneously without any specific treatment.

Neonatal outcome

Neonatal outcomes are shown in Table 6. All the parameters including mode of delivery, Apgar scores and birth weight are comparable in both groups and has no statistically by significant difference. There were no congenital anomalies in this study.

DISCUSSION

In the present study, the results showed a marked and statistically highly significant superiority of the treatment with Trihydroxyrutosides, at a dose of 600 mg/day for 2 and 4 weeks, compared with placebo. This was apparent both from the viewpoint of the patients' own assessment of their symptoms and the doctors' evaluation which also took into account the objective findings on procto-

Table 6. Neonatal outcome.

Neonatal outcome	HR (n = 27)		Placebo (n = 26)		P-value
	n	%	n	%	
Mode of delivery : number					
Spontaneous	26	96.3	25	96.2	0.98
Cesarean section	1	3.7	1	3.8	0.98
Apgar score : mean ± SD					
1 minute	8.85 ± 0.36		8.85 ± 0.37		0.91
5 minutes	9.96 ± 0.19		9.92 ± 0.27		0.22
Birth weight : grams	2890.74 ± 98.13		2850.38 ± 110. 98		0.86

scopy. The improvement of symptoms seemed to show earlier than objective findings since its results showed better outcomes after 2 weeks of treatment while the objective findings were not different in both groups, However, after further 2 weeks of treatment, the results showed improvement of both symptoms and objective findings. This may well be explained by the objective findings of the patients showing only slight changes during the 2 week period. The anorectal surgeon required more time to detect the mark differences of objective findings.

The authors were rather surprised by the very low placebo response in this indication, but may be explained by the progressive nature of untreated heamorrhoids in a continuing pregnancy.

The tolerability of the drug was good, with only 1 patient having minor and transient side effects.

Concerning the safety of the drug, there were no drug-related problems in the pregnancies, delivery or the babies. These findings were the same as other investigators who have studied the use of Trihydroxyethylrutosides in pregnancy, whether in hemorrhoids[5] or in varicose problems of the legs[11,12].

We, therefore, conclude that the use of Trihydroxyethylrutosides for the treatment of hemorrhoids of pregnancy is a very effective and safe alternative to surgical procedures, and was very acceptable to the patients.

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การใช้ไตรฮัยดรอกซี่เอธิลรูโทซัยด์ในการรักษาริดสีดวงทวารหนักในสตรีตั้งครรภ์ : การศึกษาแบบสุ่มอำพรางสองฝ่ายโดยใช้ยาหลอกเป็นตัวควบคุม

วิทยา ถิฐาพันธ์, พ.บ., บรรจบ อินทรสุขศรี, พ.บ.**,*
วิริยะ เล็กประเสริฐ, พ.บ., วิรุณ บุญนุช, พ.บ.***

ศึกษาประสิทธิภาพและความปลอดภัยของการใช้ยาไตรฮัยดรอกซี่เอธิลรูโทซัยด์ในสตรีตั้งครรภ์ 53 ราย ที่เป็นริดสีดวงทวารระดับที่ 1 และ 2 (อายุครรภ์ตั้งแต่ 16–34 สัปดาห์) โดยวิธีการศึกษาแบบสุ่มอำพรางสองฝ่ายโดยใช้ยาหลอกเป็นตัวควบคุมในผู้ป่วย 2 กลุ่ม กลุ่มแรกได้รับยาไตรฮัยดรอกซี่เอธิลรูโทซัยด์ขนาด 600 มิลลิกรัมต่อวันจำนวน 27 ราย และกลุ่มที่สองได้รับยาหลอกจำนวน 26 ราย โดยให้ทั้งสองกลุ่มรับประทานยาวันละ 2 ครั้งเป็นเวลานาน 2 สัปดาห์ แล้วประเมินผลการรักษาในทั้งสองกลุ่ม หากการรักษาได้ผลดีจะหยุดการรักษา แต่ถ้าหากการรักษายังไม่ได้ผลดี จะให้ยาต่ออีก 2 สัปดาห์แล้วประเมินผลการรักษาอีกครั้งเมื่อสิ้นสุดสัปดาห์ที่ 4 ของการรักษา ตัวชี้วัดความสัมฤทธิ์ผลของยาได้แก่ อาการ (อาการปวด การมีเลือดออก อาการคันและการมีสารน้ำเอ๊กซูเดท) และการตรวจพบอาการแสดงจากการส่องตรวจทางทวารหนัก (การมีเลือดออก การอักเสบและการขยายตัวของแขนงหลอดเลือดดำฮีโมรอยด์)

จากการศึกษาพบว่า ภายหลังการให้ยาไตรฮัยดรอกซี่เอธิลรูโทซัยด์ 2 สัปดาห์ ผู้ป่วยมีอาการของโรคดีขึ้นอย่างชัดเจนเมื่อเทียบกับกลุ่มที่ได้ยาหลอก แต่การตรวจพบอาการแสดงไม่แตกต่างกัน และเมื่อให้การรักษาต่ออีก 2 สัปดาห์ พบว่าทั้งอาการของโรคและการตรวจพบอาการแสดงในกลุ่มที่ได้รับยาไตรฮัยดรอกซี่เอธิลรูโทซัยด์ดีขึ้นอย่างชัดเจนเมื่อเทียบกับกลุ่มที่ได้รับยาหลอก ในการศึกษาครั้งนี้มีผู้ป่วยเพียง 1 รายที่มีผลข้างเคียงจากยาโดยมีอาการคลื่นไส้เพียงเล็กน้อย และหายได้เองโดยไม่ต้องให้การรักษา นอกจากนี้ยังไม่พบว่ายาไตรฮัยดรอกซี่เอธิลรูโทซัยด์ก่อให้เกิดปัญหาหรือภาวะแทรกซ้อนต่อการตั้งครรภ์ การคลอด หรือต่อทารกในครรภ์แต่ประการใด

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วิทยา ถิฐาพันธ์, บรรจบ อินทรสุขศรี, วิริยะ เล็กประเสริฐ, วิรุณ บุญนุช
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* ภาควิชาสูติศาสตร์–นรีเวชวิทยา,
** ภาควิชาศัลยศาสตร์, คณะแพทยศาสตร์ศิริราชพยาบาล, มหาวิทยาลัยมหิดล, กรุงเทพมหานคร 10700