VIET NAM MINISTRY OF HEALTH

NATIONAL HOSPITAL OF GYNECOLOGICAL AND OBSTERICS

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# Research: "**TO EVALUATE THE EFFECT AND POSSIBILITY OF ACCEPTING OF CRILA IN UTERUS FIBROID TUMOR TREATMENT**"

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# THE NARRATIVE OF THE RESEARCH

## Introduction

Uterus fibroma is a common condition in women between ages 30 to 50. It is related to the reproductive hormone estrogen. There is a high frequency of uterus fibroma in Vietnam as well as in the rest of the world. Fibroma is not cancer, but it can cause pain and complications for the patients [20] [17]. Removal of the uterus is the absolute method of treatment. However, surgery is not only expensive, but also effects the mental as well as physical health of patients. There are many patients with smaller fibromas, who are pre-menopausal, who have not yet had children. For them, surgery is not a good solution, and they prefer to treat by medications, hoping for a decrease in the size of the fibroma. Additional modern medical methods are hormone treatment, agonists, and blocking uterus arteries. There are some traditional medicines for treatment of fibroma in Vietnam as well as other places in the world. One such traditional Vietnamese medicine is extracted from Crinium latifolium (L.), *Trinh nu hoang cung*. Until now, there has been no scientific study of the evidence of active substances from Crinium latifolium (L.) for treatment of fibroma. According to Dr. Do Tat Loi, "Crinium latifolium (L.) has medical efficacy in the treatment of some diseases, but the active substances should be researched by systematic science [7]. Based on the scientific information, Dr. Doan Thi Nhu had considered and emphasized the same. Dr. Do Tat Loi recommended "*Clinical Trials should be conducted with a larger sample size of patient and longer duration of study, in order to fully evaluate the treatment from* Crinium latifolium (L.)*"* [9].

Dr. Tran Duc Tho, as well as other authors, state that the Crila capsule, a product from Crinium latifolium (L.), can treat effectively non malignant tumors of the prostate gland in only 2 months [6], [10], [18].

According to the regulation "Clinical Trials of Traditional Medicine" of the Vietnam Ministry of Health [1], [2], there were 10 patients who participated the primary Clinical Trial about the safety of the Crila capsule in the National Hospital of Obstetrics and Gynocology in 2004 (Phase I) and continuous 30 patients were participated in a Clinical Trial studying the decreasing dimension of uterus fibroma in 2005 (Phase II). The results are satisfactory [20]. Therefore the overall request of evaluation about safety as well as efficacy of the Crila capsule with a large sample size, longer duration of treatment, conducted at multi-centers, is a

scientific essential for the study of traditional medicine. We are conducting the Third Phase of Clinical Trial for medical properties of the Crila capsule in uterus fibroma.

**General objectives:**

According to the Vietnam Ministry of Health, the Third Phase of the Clinical Trial for traditional medicine, is conducted for the the purpose of proving by scientific evidence, the ***"medical efficacy, safety and side effects"*** in the patients with uterus fibroma using the Crila casule (the product extracted from Crinium latifolium (L.).

***Specific objective:***

1. To evaluate the efficacy of reducing the dimension of uterus fibroma and physiological signs of the patients after using 3 continuous stages of treatment in 90 days.
2. To evaluate the safety, tolerance, and side effects of patients who were treated orally by CRILA capsules.

The objectives were proven.

- Uterus fibroma is effectively treated by the CRILA capsule
- CRILA capsules were well tolerated by patients for safety and without significant side effects.

# Chapter 1
# *BACKGROUND*

## 1.1. OVERVIEW OF UTERINE LEIOMYOMA (UL)

Uterine Leiomyoma (fibroid) is a benign tumor in uterus which usually occurs in women aged 30-50. There are many hypotheses on pathogenesis of Uterine Leiomyoma, in which hyperestrogenism are supported by many authors [5,18].

### 1.1.1. Pathogenesis of Uterine Leiomyoma

There are many evidences to show that uterine leiomyoma is related to female gonad hormones because UL does not appear before adolescence and UL degenerates after menopause. Furthermore, ULs have receptors for gonad hormones (estrogen and progesterone) and develop very fast during pregnancy when blood estrogen and progesterone concentrations are high.

Relative hyperestrogenism stimulates protein synthesis in uterine muscle. During pregnancy, estrogen activates actinomyosin and causes uterine muscular cells to develop. By experiments, some authors found out that high doses of estrogen caused uterine leiomyoma.

Role of growth hormone (GH) It is observed that blood GH concentration is high in women with UL. Experiments on animals (female rats with pituitarectomy and ovarectomy) showed that GH combined with estradiol can increase uterus volume.

### 1.1.2. Pathology of UL

- *Macroscopic:*

ULs are round or oval, firm, and have a capsule; therefore there is a distinct separation between the tumors and normal uterine muscle. On dissection, the tumor is white. The tumor consists of smooth muscle nourished by outside vessels and nutrients penetrate through the membrane of the tumor. Occasionally, tiny vessels come deeply into the center of the tumor. As a result, the tumor is permanently undernourished and becomes aseptic necrosis. The number of nuclei in ULs are variable- some have only one big nucleus, while the others may have small or moderate-sized multiple nuclei. Location of the tumor is also different from one individual to another.

- *Microscopic:*

UL is formed by concentric muscular fibers. Cellar nucleus is oval or round and muscular fibers interpose. Tumor cell has a round or oval nucleus with proportional nucleus/ protoplasm ratio. Connective tissue intermixes with smooth muscular fibers. After menopause, the smooth muscular fibers decrease in number and are replaced by collagenoid fibers and calcification. Vasomotor disorders result in microscopic degeneration of the tumor. Degeneration is often caused by partial venous occlusion. Occlusion results in softening of the tumor and separation and destruction of muscular fibers tumor. Finally, aseptic necrosis occurs.

+ *Hyaline degeneration:* is a result of the loss of muscular fibers and connective tissue. The whole tumor then becomes a transparent and acellular mass. If complete embolization occurs, the tumor becomes mucous or collagenoid.

+ *Septic degeneration*: in cases of long pedunculated tumors (that tends to twist and necrotic) or injuries, bacteria invade into the tumor and cause septic necrosis.

+ Vascular spasm may cause occlusion and infarction and leads to necrosis. If infarction is limited, the tumor will become edematous and muscular cells lose its nuclei. If the infarction expands, tumor turns black and is like well-done meat and discharges a pale red liquid.

+ *Calcification:* at the end of necrosis, calcium accumulates at the center of the tumor and between muscular fibers. Calcification may be at the center of the tumor and expands; in this case the tumor becomes hard and can be detected by X-rays or ultrasonography.

+ *Malignant degeneration*: rare and usually begin at the center of UL. UL becomes soft, lesions diffuse, the limit between the tumor and normal area is obscured and there is hemorrhage. The tumor is difficult to be dissected. Microscopic examination shows abnormal cells with multiple dividing nuclei.

### 1.1.3 Location of ULs

Anatomically, ULs may occur in the body, isthmus, fundus, or cervix. The rates are 96%, 3%, and 1%, respectively.

- If located in fundus, ULs often bulge in the abdominal cavity. Fibroid may be subperitonial, intramural or submucosal.
- In uterine isthmus, the tumor grows in pelvis and compresses bladder or rectum. ULs may grow into broad ligament and compress nerves, blood vessels or change normal anatomical site of ureter.
- ULs in cervix often grow towards vagina. ULs in posterior wall may grow to Douglas cul-de-sac and compress rectum. Tumors in uterine anterior wall may expand to pelvis and compress bladder and urethra. Tumors may become pedunculated and reach to uterine orifice and obscure orifice. Polyp of uterine may occur**.**

### 1.1.4 Clinical manifestations and imaging findings

* *Clinical manifestations*

- Symptoms: bleeding is the main symptom and occurs in 60% of cases. Symptoms are menorrhagia or hypermenorrhea with profuse menstrual flow that may include clots and cause anemia. Occasionally, patients experience a heavy sensation in lower abdomen or pelvis which increases during period. Profuse and water-like leucorrhea may occur.
- On physical examination: uterine fundus can be palpable. The mass is in the middle line, mobile, firm and dull on percussion. Vagina combined with abdomen examinations show enlarged, firm and smooth uterus. Occasionally firm and tenderless masses can be felt on uterine surface. Masses are movable when moving cervix. Rectal examination helps to differentiate ULs that grow forward or rectal tumors. ĐO BUỒNG Tử CUNG is little of value, but this may reveals BUỒNG Tử CUNG is longer than normal.

* *Imaging diagnosis*

- Ultrasound (US) reveals homogenous and hypoechoic appearance. Differential diagnosis by US may be difficult in case of cystic ovaries that attach to uterus. Subserosal ULs change the shape of uterus and are the most easy to realize. However, pedunculated tumors can be mistakenly diagnosed as solid tumor of ovaries.
- Radiology investigation of uterine lumen is usually required because this provides direct information about the tumor and accompanying lesions such as hyperplasia of uterine mucosa or cancer of fundus uteri.

- Endoscopy of uterine lumen - when the tumor is small or submucosal, it is easier to observe by endoscopy.

### 1.1.5. Progression and complications

- Degeneration- often occurs in small tumors, after pregnancy and especially after menopause when ovaries cease to secrete estrogen.
- Hemorrhage- often occurs in submucosal ULs. Hemorrhage is common symptom and complication of ULs that causes menorrhagia and hypermenorrhea. Hemorrhage is a result of hyperplasia of uterine mucosa caused by estrogen-progesterone imbalance (which well responses to progesterone treatment), atrophy of uterine mucosa, disturbance in response of uterine mucosa to estrogen, or ulceration or infection of submucosal ULs. Prolonged bleeding may cause chronic hypochromic anemia, confirmed by CBC count and hemoglobin.
- Pressure- This is a common complication. When an UL enlarges, it may compress adjacent organs. Severity of the complication depends on the growth of tumors. If an UL expands to the broad ligament, it will compress the ureter and may causes pyeloectasis. The tumor may compress the rectum and results in chronic constipation or rectal obstruction. ULs can be stuck in pelvis and compress arteries and veins; as a result, edema in lower extremities may occur.
- Torsion-occurs in subperitonial pedunculated tumors and manifested by rigorous pain in pelvis and signs and symptom of peritoneal irritation, abdominal pain and distention, elevated pulse rate and shock.
- Infection is rare and usually occurs in submucosal ULs or polyps that protrude into cervix. Patients will have fever, abdominal cramp, elevated WBC.
- Degeneration- ULs may degenerate, in which hyaline degeneration is the most common. Aseptic necrosis may be caused by circulation disorders inside the tumor. The tumor then becomes red, edematous and hemorrhagic. Hemorrhage dissects muscular fibers. Calcification may occur and can be shown on conventional abdominal X-rays.
- Obstetric complications- ULs may cause infertility, abortion or preterm birth. ULs may cause abnormal fetal presentation or become tumor previa. During pregnancy, ULs may infiltrate, enlarge and soften; these may cause aseptic necrosis.

### 1.1.6 Treatment of ULs

- ***Follow-up***- In case of asymptomatic ULs, ULs smaller than 8cm, patients are unwilling to be operated or operation needs to be postponed.
- ***Surgical intervention*** is the radical treatment. Indications for surgery include large tumors, evidence of pressure, vigorous bleeding, hypermenorrhea or menorrhagia causing anemia, pedunculated or submucosal tumors, or tumors get stuck in pelvis. Two surgical procedures are often used depending on the patient's preference:
    + *Dissection of UL (fibroid):* tumor dissection with preservation of reproductive function. There are risks of post-operative hemorrhage and recurrence of the tumor.
    + *Partial or complete hysterectomy:* the basic and radical surgery and can be perform via abdomen incision or endoscopy. Complete hysterectomy prevents malignant degeneration and cancer at the remaining cervix. Partial hysterectomy is indicated in young women who want to keep the cervix. However, it is required to confirm that there is no lesion in cervix before operation and regular cytological examination after operation.

- ***Medical treatment***

Because causes of ULs are unknown, there is no specific medical treatment. However, because theory on estrogen is accepted, estrogen antagonists can be used. Drugs often used are:

+ LH-RH like agonists: commonly used drugs in treatment of ULs are estrogen antagonists (progresterone or LH-RH like drugs such as Decapeptyl or Zoladex). These drugs inhibit pituitary gland to secret FSH; as a result, ovaries do not secret estrogen and ULs will shrink. However, medical treatment cannot replace surgery because efficacy is unstable and temporary. ULs often enlarge and obtain initial size after 6 months of discontinuation. Furthermore, cost of treatment is high and there are many disadvantages such as flaring, vaginal dryness and increased risk of osteomalacia if drugs are used for a long time.

+ Progesterone is also a drug for treatment of ULs. Until now, there is no evidence to show that the drug has an effect on uterine smooth muscle, but on uterine epithelium, the drug prevents hyperplasia that contributes to prevent uterine carcinoma and alleviate menorrhagia.

+Testosterone antagonizes to estrogen and decreases congestion, therefore decreases menorrhagia. Mechanism of action of testosterone is antagonizing action to estrogen. According to some authors, testosterone inhibits the secretion of gonadotropin in pituitary gland, therefore decreases estrogen secretion in ovaries.

- **Radiotherapy**

X-rays or radiation (Radium) are used in case surgical intervention is infeasible because of poor general status, heart or kidney disease, or diabetes mellitus. X-rays make the ovaries atrophic, therefore causes artificial menopause. Radium directly affects on the tumor, destroys fibrous tissue and therefore makes the tumor shrink. However, this treatment is not often used because of ovary atrophy in young women and adverse effects of radiation.

- A new method in treatment of ULs is to introduce a chemical via femoral artery to obstruct the two uterine arteries; this cause undernourishment of the tumor and ultimately decreases the size of the tumor. However, this method has many disadvantages, particularly in decreasing blood flow to ovaries and leads to precoce ovary failure (the rate is from 5 to 10%, mostly in women after the age of 40.)
- **Traditional medicine uses some drug formulas to treat ULs**. One of these is extracts from *Crinum latifolium L.* in combination with *Panax pseudoginseng Wall.* However, there is no systematic study but only experience on using *Crinum latifolium L* for treatment of Uterine Leiomyoma.

## 1.2 STUDY ON *CRINUM LATIFOLIUM L.* IN TREATMENT OF ULS

1.2.1 Crinum Latifolium L.

*Figure 1.1 Crinum Plant*

*Crinum latifolium L* grows in several Asian countries such as China, India, Thailand, Cambodia and Vietnam. *Crinum latifolium L* is a grass species, belongs to Amaryllidaceae family with 120 species in tropical area. In Vietnam, common species are *Crinum latifolium L., Crinum asiaticum L.,* and *Crinum ensifolium Roxb.* There are also three other species: *Crinum gigantium Andr., Crinum moorei Hook* (which has origin from Africa), and *Crinum amabile Donn.*
*Crinum latifolium L.* has a bubble like trunk, spherical root of 10-15 cm in diameter, its ocreas together constitute a trunk of approximately 10-15 cm. Its leaves are thin and 80-100 cm long with wavy edge of 3-8 cm in length and the veins of the leaf are parallel. The superior surface of the leaves is concave and forms a furrow. Ribs of the leaves are clear and on the inferior surface. Heads of ocreas near the ground are purple. The flowers grow in raceme of 6-8 flowers on a 30-60 cm long limb. Petals are white-pinkish with purple spots. The part to use as a drug is leaves.

According to traditional medicine, *Crinum latifolium L.* is pungent, cool, little toxic. ***Its characteristics are vitality motivation, anti-inflammation, pain relief, heat eradication, detoxication, blood activation, and can cure tumors.*** *Crinum latifolium L.* has been used by ***royal physicians*** to treat gynecological disorders for imperial concubines including dysmenorrheal and tumors. Because most concubines did not give birth to a baby, this plant is called by the name Trinh Nu Hoang Cung (***Imperial Virgin, or Virgin in the Palace***) This plant is also used among common people to treat several urinary diseases.

1.2.2. **Studies on *Crinum latifolium L.***

- **International studies**

- In 1984, Ghozal et al. (India) extracted latisoline, a glucoalkaloid in the limb of *Crinum latifolium L.* An aglycon, lanasodine was also extracted when hydrolyzing parts of *Crinum latifolium L.* Furthermore, Ghozal and Shipnath have extracted pratorimine and pratosine, two new alkaloids along with Ambeline and Lycorine , two known substances from the bubble of flowering *Crinum latifolium L.*[21,22].

- In 1986, Ghozal et al. announced to extract some alkaloid derivatives from *Crinum latifolium L* which have antitumoral, antiviral and immunostimulating characteristics. Of which, lycorin, the main active ingredient, decreases vitality of tumor cells [22,23].

- In 1988, P. Zajac et al. proposed that extracts from *Crinum latifolium L* strongly stimulate CD4(+) and CD8(+) T cells and production of human- TNF-α- like tumor destroying substances [24].

- In 1998, Yui et al. showed that lycorin, the main alkaloid from *Crinum latifolium L* has T cell stimulating feature [25].

  - **Domestic studies**

- ***Nguyen Thi Ngoc Tram*** et al. (2001) showed that segment CW262 of *Crinum latifolium L* leaves contain eight alkaloids with strong activity on three tested cells originating from cancer cells: Hep-G2 (skin cancer cell), F1 (uterine endothelial carcinoma) and RD (myocardial sarcoma) [11,12].

- ***Nguyen Thi Ngoc Tram et al.*** (2000) showed that hot water extracted substances from *Crinum latifolium L.* activate the reproduction of T cells and particularly directly stimulate CD3 T cells. Besides the above activities, extracts from *Crinum latifolium L* also have antibacterial and anti-inflammatory activities. Therefore, common people often use ground roots of *Crinum latifolium L.* to apply on inflammatory and infectious skin to treat furuncle [15,16].
- Findings from a study of Nguyen Xuan Huong in 2001 showed that extract of *Crinum latifolium L* has good effect in treatment of benign prostate hypertrophy.

- A study of efficacy Pham Khanh Bien (2005) (efficacy of *Crinum latifolium L.* capsule in treatment of benign prostate hypertrophy) showed that the drug decreased prostate size and highly improved urination disorders.

### 1.2. Mechanism of action of *Crinum latifolium L*

#### 1.3.1. Alkaloids in *Crinum latifolium L*

Until now, scientists have identified 16 alkaloids from *Crinum latifolium L* Chemical composition of *Crinum latifolium L* includes glucanes, organic acids, saponin, aminoacids and alkaloids. Glucanes includes glucanes A and B. Aminoacids includes phenyllalamine, L-leucine, DL-valine, L-arginine monohydrocloride.

Based on chemical structure, alkaloids from *Crinum latifolium L* are classified into two groups:

- Non- heterocyclic alkaloids such as latisoline and latisodine
- Heterocyclic alkaloids such as ambeline, paratorimine, pratosine, beladine

In 2002, by chromatography, Nguyen Thi Ngoc Tram extracted an dihydro-oxo-demethoxyhaemanthamine, an heterocyclic alkaloid with a loose nitrogen connection to R radicals at the sites 11 and 12 of Me functional group (which replaces $H^+$) , from the leaves of *Crinum latifolium L.*. Furthermore, when changing the Me functional group, she obtained other analogues and alkaloids with different activities.

Also according to Nguyen Thi Ngoc Tram, extraction from the leaves of *Crinum latifolium L.* at segment CW 262 has 8 alkaloids in which alkaloids #6 and 7 have tumor inhibiting activity via immumological system stimulation; while as alkaloids # 8 (crinafoline) has direct inhibitory activities on tumor cells and therefore decreases tumor size. Besides the above activities, extract from the leaves of *Crinum latifolium L.* has antibacterial and anti-inflammatory activities. This explains why common people often use grond root of, from the leaves of *Crinum latifolium L.* to apply on infectious areas to treat furuncles.

- In 2001, Nguyen Thi Ngoc Tram et al. showed that lycosin, an alkaloid extracted from *Crinum latifolium L.,* is the main substance to stimulate T cells in vitro and on experimental rats and decrease vitality of tumor cells. Furthermore, hot water extract from the leaves of *Crinum latifolium L.* decreased tumor size on experimental mice.

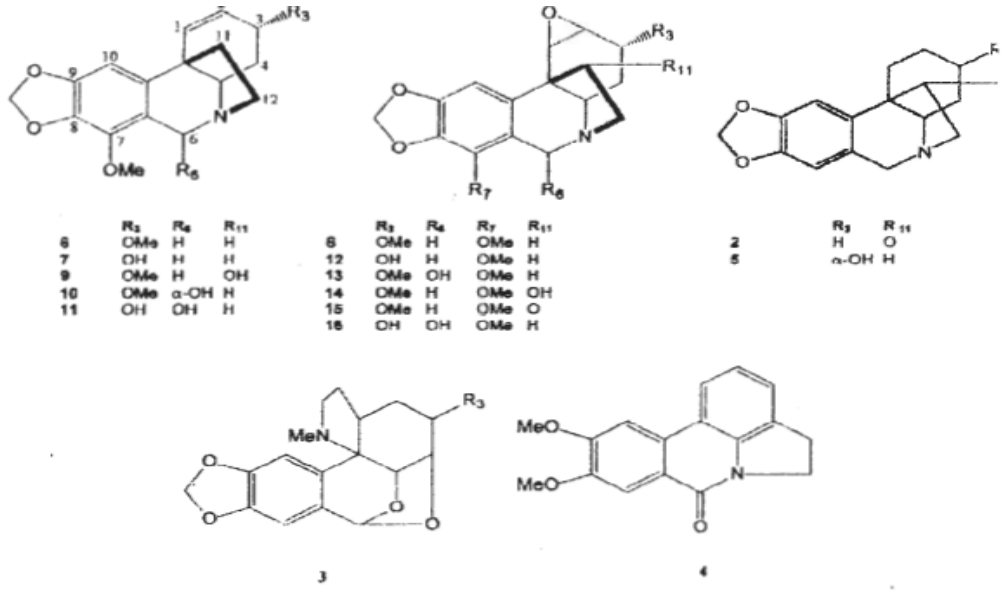
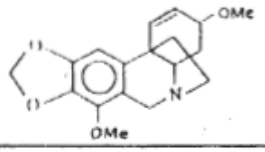
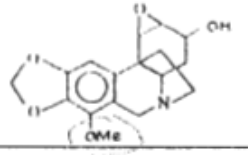
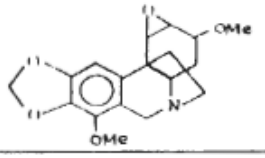
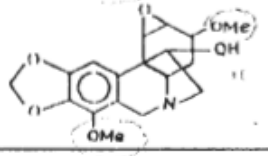
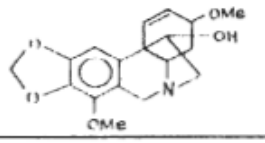
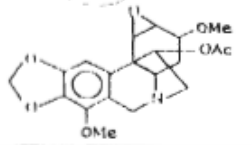
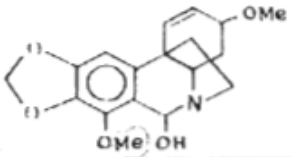
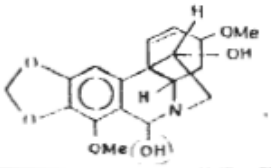



Fig. 1. Alkaloids in *C. latifolium* leaves: dihydro-oxo-demethoxyhaemanthamine (2), augustamine (3), oxoasso (4), crinane-3α-ol (5), buphanidrine (6), powelline (7), undulatine (8), ambelline (9), 6-hydroxy-buphanidrine 6-hydroxypowelline ( ), crinamidine ( ), 6-hydroxyundulatine ( ), 1β β-epoxyambelline ( ), epoxy-3,7-dir oxycrinane-11-one (tentative) ( ), 6-hydroxycrinamidine (

**Figure 1.2.** *Formula of alkaloids with heterocyclic nuclei* ***(dihydrro-oxo- demethoxyhaemanthamin****) and Me function from Crinum latifolium L.*

- In August 2003, via a trial for subacute toxicity of *Crinum latifolium L.* on 24 rabbits using *Crinum latifolium L.* for two months at Department of Experimental Traditional Medicine, National Hospital of Traditional Medicine, Nguyen Thi Ngoc Tram et al. showed no significant changes in hematological and biochemical indices, compared to those of before the trial. In September 2003, Nguyen Thi Ngoc Tram et al. tested acute toxicity of *Crinum latifolium L.* at the Research Unit, Department of Traditional Medicine, Ho Chi Minh City University of Medicine and Pharmacy and concluded that LD50 is 49.7mg/kg on mice[3].

*Các alcaloid có trong phân đoạn CW 262 chiết từ lá cây trinh nữ hoàng cung.*

| STT | Tên chất | Công thức | STT | Tên chất | Công thức |
|---|---|---|---|---|---|
| 1 | Buphanidrin |  | 5 | Crinamidin |  |
| 2 | Undulatin |  | 6 | 1,2-Epoxy-ambellin |  |
| 3 | Ambellin |  | 7 | 11-Acetoxy 1,2-Epoxy-ambellin |  |
| 4 | 6-Hydroxy-buphanidrin |  | 8 | Crinafolin |  |

Line above the table Fig. 1.3, *Alkaloids in segment 262 extracted from Crinum latifolium L.*

**Figure 1.3.** *Main alkaloids from Crinum latifolium L.*

### 1.3.2. Concepts of UL in Oriental Medicine

In Oriental medicine, tumor is a disease caused by disorders of vitality functions and seven feelings (joy, anger, love, hate, sorrow, passion, and lust) of the Five Organs in the body. These result in a vitality stagnation that accumulates in the body and form the tumor. Based on that concept, principle for treatment of tumors in traditional medicine is "kien gia tieu chi" (which means that to make hard tumors disappear) and "lieu da cong chi" which means using attacking method to treat tumors, such as "nhuyen kien" (meaning to make tumors soften and dissolve) [17].

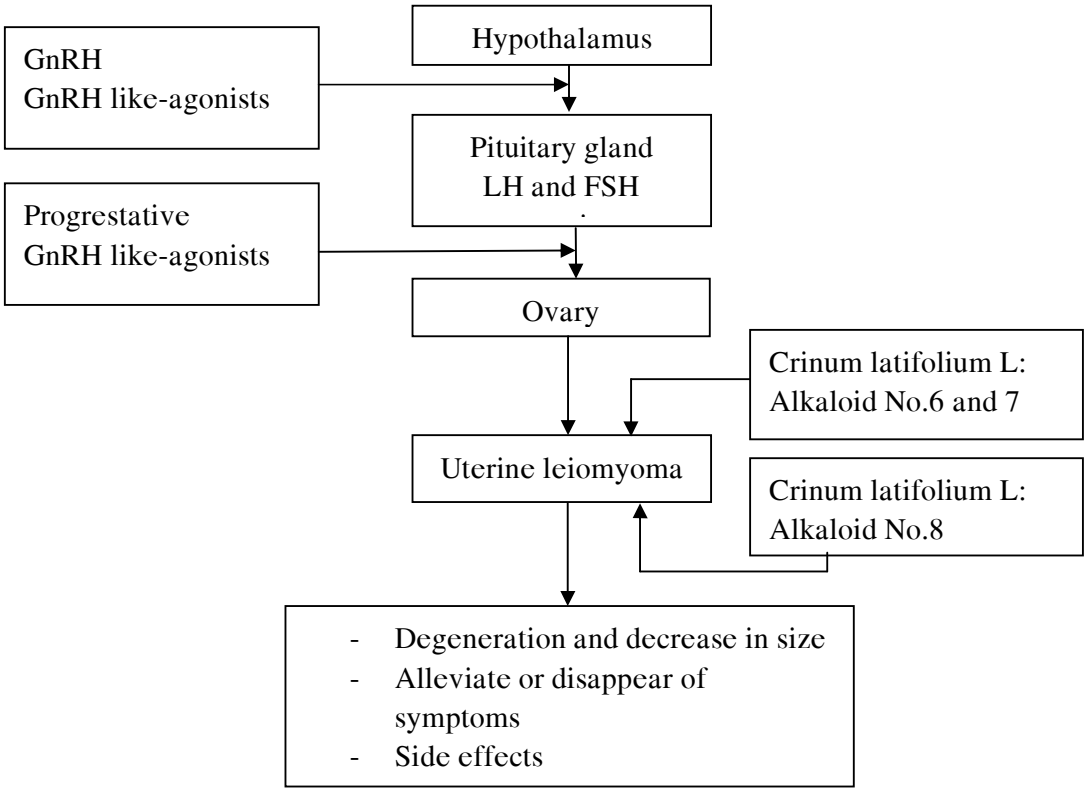
Current Chinese medicine concepts that ULs are caused by writhing mood, irregular blood circulation, indomitable spirit asthenia, vitality stagnation, all of these accumulate to form unmovable masses and result in tumors after a long time. Causes of the disease are numerous, but the main cause is vitality stagnation. Based on the chronicity, the disease is classified as the real and unreal. Diseases at the onset are the "real", while most chronic diseases are "unreal".

Etiology of the disease is the accumulation of damaged vital force and stagnated blood flow in the uterus after a long time or irregular movement of spleen and stomach "functions", this causes an accumulation of liquid to form mucus. Mucus then in its turn to accumulate in the uterus and finally a hard tumor which gradually enlarges and causes pain and dysmenorrheal.

### 1.3.3. Hypothesis of effect of *Crinum latifolium L.* in treatment of UL

Based on the experiments of *Crinum latifolium L.* on esophageal cancer in mice and clinical trials on human in treatment of prostate adenofibroma (fibroma) [9,10,11], a hypothesis was proposed (Chart 1.1)

**Chart 1.1. Hypothetical effect of Crinum latifolium L. in treatment of UL**




### 1.3.4. Results of phase I and phase II clinical trials

Clinical trials on Crila® capsule in treatment of uterine leiomyoma at the National Hospital for Gyneco-Obstetric Disease in 2004

***Phase I***- to preliminary efficacy of the drugs (conducted on 10 volunteers) and evaluate suitability of treatment schedule (dosage and time interval between doses) and adverse events.

***Phase II***- to evaluate efficacy, safety, side effects and tolerability (conducted on 30 patients.) Efficacy was evaluated by disappearance of the tumor, decrease in size of the tumor, disappearance of signs and symptoms, rate of side effects, and tolerability [4].

***The findings of the studies are as follows:***

1. **Safety-** Crila® capsule, manufactured from extract of *Crinum latifolium L.* by the Central Pharmaceutical Company II has been tested for toxicity on animals and humans. Results showed that the drug is at the dose of 8 capsules (equal to 0.2g raw product/kg/day) a day. No medically significant adverse events were found over 3 consecutive treatment courses. No statistically significant difference in CBC count and liver and renal function test results before and after using drug.
2. **Efficacy**- tumors reduced size in 66.5% of cases. Treatment with Crila® capsule also showed an improvement in menorrhagia/ hypermenorrhea caused due to ULs.

3. **Tolerability**- the drug was highly tolerated by patients because of no toxicity, high level of safety, few side effects (which tended to reduce in the next treatment course.) Crila® capsule is easy to use, does not cause discomfort and is at a reasonable cost.

***Recommendations***

(1) A study with larger sample size and better design to reduce potential biases such as measurement biases (ultrasound, for instance) and lost to follow-up.
(2) Even though reduced tumor size in 66.5%, extent of size reduction needs to be investigated. Impact of reduction of tumor size r(and therefore decrease of surgical intervention) also needs to be investigated.
(3) Crila® capsule can be used in treatment of uterine leiomyoma if the next study shows similar findings (according to Ministry of Health's regulations.)
(4) To establish a treatment regimen with higher dose to evaluate efficacy of the drug

# Chapter 2

# STUDY POPULATION AND METHOD

This is the phase III clinical trial (expanded clinical research- according to Ministry of Health) on Crila® capsule in treatment of uterine leiomyoma. Therefore the study on a larger scale to confirm evidences on efficacy of the drug in the previous phase I and phase II clinical trial while complying to criteria of the phase I and phase II trials with complements and amendments to clarify study findings in order to make a scientific conclusion to obtain a license for manufacturing and circulating the drug.

## 2.1. STUDY POPULATION

Women visited for gynecological examination were diagnosed with uterine leiomyoma at the National Hospital of Gynecological and Obsterics, Tu Du Hospital of Gynecological and Obstetrics in Hanoi, and Hospital for Traditional Medicine in Ho Chi Minh City from August, 2006 to July, 2007.

### 2.1.1. Inclusion criteria:

- Clinically confirmed diagnosed that uterus is smaller than the uterus of 12 week gestation.
- One UL with muscular nucleus 2-6 cm in diameter confirmed by ultrasonography. The rationale is that if the diameter is lower than 2 cm, it is difficult to correctly measure the size; if the diameter is higher than 6 cm, complications occur commonly or the patients' prefer surgical intervention, or if the patient wants to have a baby, dissection of the nucleus is indicated.
- Patients still have periods.
- Patients consent to the study and agree to comply with study requirements, including pre-scheduled visits.
- Clear address to contact.

### 2.1.2. Exclusion criteria

- Tumors larger than 6 cm or smaller than 2 cm or ULs causes health problems such as menorrhagia/ hypermenorrhea, significant abdominal cramp that affects patient's health status.
- Menopause.
- Anemia (Hb<100g/L)
- Accompanying diseases such as ovarosalpingitis, infertility, or pregnancy
- Diseases at the presentation: heart disease, liver or kidney disease, coagulation disorders, hypertention, history of allergy to drugs or food.
- Suspected signs and symptoms of uterine cancer such as bloody leucorrhea, rapid weight loss, soft and enlarged uterus, UL is not found.

### 2.1.2. Criteria for study discontinuation

- Increase in severity of symptoms that affect patient's health.

- The patient does not visit and receive study drug.
- Patients decide to leave the study.

## 2.2. STUDY DRUG: CRILA® CAPSULE

- Study drug, known as the trade name *Crila®,* was hard capsule with active ingredient extracted from whole alkaloids of *Crinum latifolium L.*

- A capsule contains 1.25 mg alkaloid from *Crinum latifolium L.* manufactured by Center for Research and Manufacture for Crila® (short name "Center for CRILA"), National Traditional Drugs Joint-Stock Company No. 2. The drug was approved by Ministry of Health on June 6, 2002. Study drug used in this study was provided (free of charge) by the National Traditional Drugs Joint-Stock Company No. 2.

- National Traditional Drugs Joint-Stock Company No. 2 has responsibility to ensure the quality of study drug and legal status of approved documents according to regulations of Ministry of Health.

Dosage: 10 capsule/day in 9 weeks.


**Figure 1.4.** *Crila® capsule.* Manufactured by National Traditional Drugs Joint-Stock Company No. 2 from dry extract of *Crinum latifolium L.*

## 2.3. METHOD

*Study design:* ***clinical trial to compare signs and symptoms before and after intervention, with compliance to "Regulations on evaluation of safety and efficacy of traditional medicine" [1].***

- Patients were examined to confirm UL. Ultrasonography was performed to ensure the diameter from 2-6 cm. If the patient participates in the study, detail study medical record, hematological and biological tests will be performed. (Appendix 1.) After completing study medical record and tests, the patient will use study drug following below instructions.

***Treatment course***

*First visit*

- Interview, examination, ultrasound, blood tests, review of study criteria and filling of "***First Visit Follow-Up Form***"

- First course treatment: providing 210 Crila capsules for a patients and gave instructions to the patient: ***taking 10 capsules a day, divided in 2 doses, 1one hour after meal.*** Study drug was used for 21 consecutive days (3 weeks.)

*Second visit*

- After taking all drug for the first course, the patient come for the second visit, examined following similar procedures as the first visit. "***Second Visit Follow-Up Form***" was filled out and a patient was ***provided 210 Crila capsules for 21 consecutive days (3 weeks.)***

*Third visit*

- After taking all drugs for the second course, the patient came for the second visit, examined following similar procedures as the first visit. "***Third Visit Follow-Up Form***" was filled out and a patient was ***provided 210 Crila capsules for 21 consecutive days (3 weeks.)***

***One month after the last dose of the third treatment course, the patient was examined and final blood tests were performed. Therefore, patients took three treatment courses (630 capsules in total) and were examined and had blood test for the fourth time.***

## 2.4. DATA COLLECTION

- Individual characteristics: age, address, obstetric history.
- Menstrual status: relative amount of blood (redundant, moderate, little) based on patient's description.
- Cramp: severe (need to take a rest or use an antispasmodic); moderate (cause discomfort but no need for rest or drug) and mild (heavy sensation in lower abdomen but not affect normal activities).
- Adverse events such as headache, nausea, breast tension, dizziness, urination symptoms, flare and vaginal dryness. Severity of the symptoms were classified as serious (symptoms affect normal activities and need intervention), moderate (symptoms cause discomfort and draw patient attention) and mild (cause little upset).
- Data on potential adverse events: Pulse rate, blood pressure, CBC count and biological indices (SGOT, SGPT, blood urea and creatinin).

***Ultrasound technique***

***Since ultrasound (US) were performed in three different health care facilities, we performed bilateral ultrasound diagnosis using equipment with as similar parameters as possible.*** Because we needed to evaluate the effect of the tumor on other viscera in pelvis, we used abdominal probe when the bladder is full. We changed position of the probe and observed on many sections to determine horizontal and sagital sections of the muscular nucleus. US image of the nucleus is an echoic with a capsule which is different from normal uterine muscle. ***Tumor diameters were measured inside the capsule. Size of the nucleus on US is the average of horizontal and sagital sizes.*** US were only performed by two study doctors from the beginning to the end of the study. US images were saved in computers.

If a patient experiences menrrhagia or hypermenorrhea, she will discontinue using study drug and leave the study.

## 2.5. SAMPLE SIZE AND DATA ANALYSIS

Sample size was calculated using "Adequacy of Sample Size in Health Studies" (WHO, 1990) as follow:

$$n = \frac{\left(z_{(1-\alpha/2)}\right)^2 . p.q}{\left(d\right)^2}$$

Where:
*n* = minimum sample size
p= proportion of reduction in tumor size (66.55 in a study in 2005)
q= 1-p
$\alpha$=0.05, $Z_{1-\alpha/2}$=1.96, d=0.07

***After calculation, needed number of participants was 181. Predicted loss to follow-up rate was 10%. Therefore, the number of study participants for each hospital was from 61 to 67.***

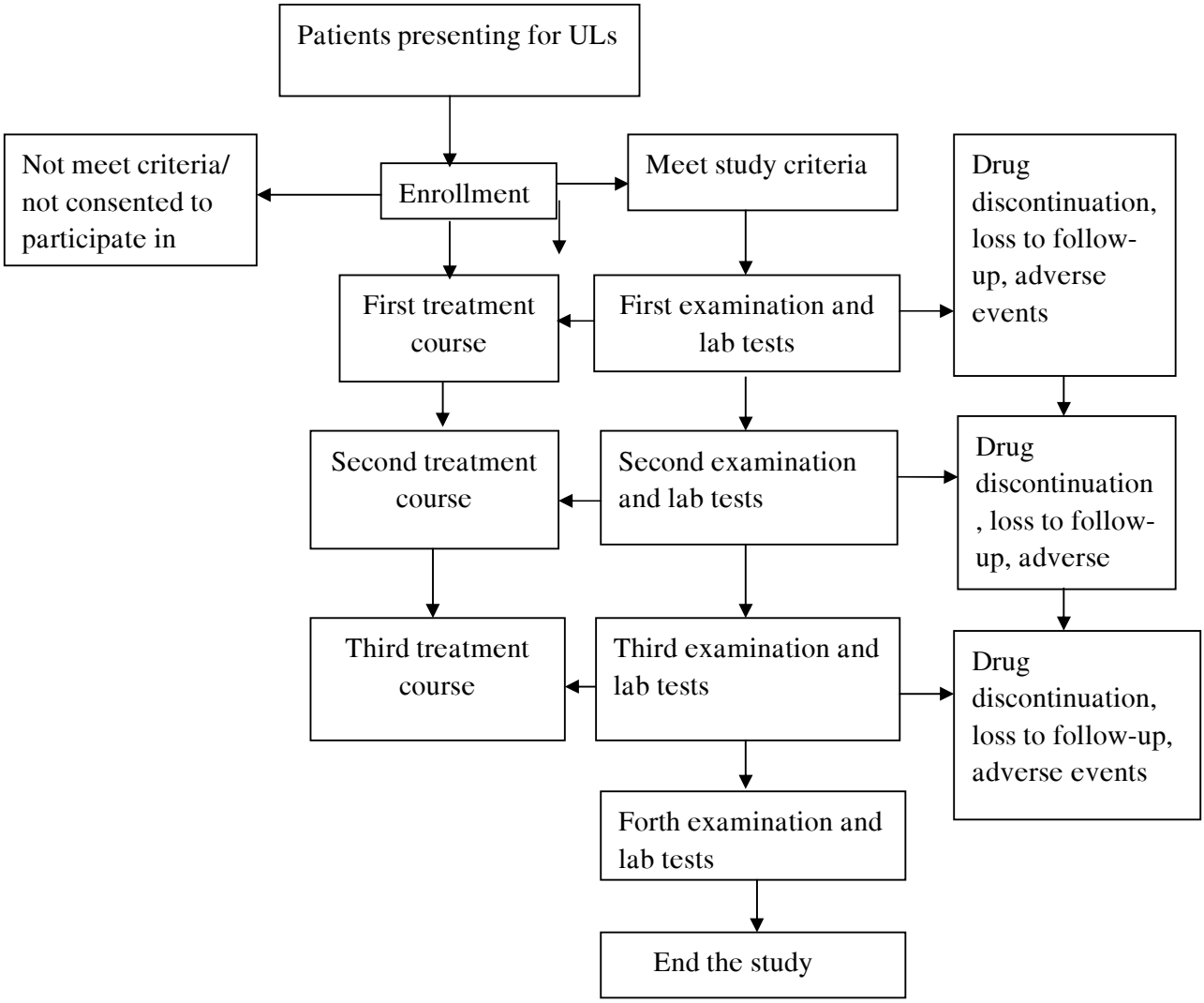
***Potential biases***

***- Bias due to US (measurement bias):*** efficacy of the study drug was shown by reduction in tumor size (measured via ultrasound) after three treatment courses; therefore tumor size needs to be strictly measured. Bias may occur if many doctors perform ultrasonography (ultrasound) for one study participant over visits. To avoid this type of bias, each patient was only investigated by one or two doctors throughout study time.
- ***Loss to follow-up*** occurred in several study participants who live far away from the hospitals or were busy, so they could not come for visits and receiving study drug. Data on those particular cases were carefully analyzed to get experience and comment.
- **Questionnaire** (see Appendix) used in the study included information on physical examination, lab test results, adverse events and changes in drug use and drug tolerability and side effects.

***Data analysis***

Collected data were coded and entered using SPSS software, version 11.5. Means were calculated and $\chi 2$ test were used to compare values before and after treatment in each hospital and three hospitals in combination and p-value.

Chart 2. Study Flow Chart



**-Evaluation of effect on reduction of tumor size**

+ ***Very good***: diameter of tumor decreases ≥ 50%, compared to initial diameter.
+ **Good**: diameter of tumor decreases 20%-49%, compared to initial diameter.
+ **Fairly good**: diameter of tumor decreases 10%-19%, compared to initial diameter.
+ **Acceptable**: diameter of tumor decreases ≤10% (no larger), compared to initial diameter.
+ **Ineffective**: tumor is larger than initial diameter.

**-Evaluation of symptoms**

Abdominal pain when having or not period, and amount of blood in menorrhea before and after treatment.

- **Evaluation of biochemical indices and several symptoms**

+Pulse and blood pressure.
+Biochemical indices: SGPT (ALT), SGPT (AST), blood urea and creatinin.
+Adverse events: nausea, vomiting, abdominal pain, diarrhea, headache, dizziness, vaginal dryness, and flare.

## 2.6. ETHICAL ISSUES IN THE STUDY

The results in Phase I and Phase II trials of this drug were approved by the Ethical Committee, Ministry of Health. Findings from this study are the "scientific basis for the Ministry of Health to approve submission of drug registration according to the regulations".
Study participants must be informed in detail about the study and voluntarily participate in the study by signing the **Informed Consent Form.**

Crila® capsule has been licensed to circulate nationwide to treat benign prostate hypertrophy on July 21, 2005 by Department of Pharmaceutical Products, Ministry of Health. The results in Phase I and Phase II trials of this drug were approved by Council of Science and Technology, Ministry of Health. The results in Phase I and Phase II trials of this drug were approved by the Ethical Committee, Ministry of Health. Findings from this study are the scientific basis for the Ministry of Health to approve the second indication of this drug: treatment of uterine leiomyoma.

Crila® capsules and lab tests during the study were provided free-of-charge for study subjects. Free treatment was also provided for adverse events. Subjects were also provided travelling fee for visits during the study.
Information obtained from interviews and physical examination of the subjects was kept confidential. Names and addresses of study participants will be not disclosed in any way and only served for communicating to study participants during the study [20].

# Chapter 3

# RESULT OF STUDY

## 3.1 COMMON FEATURES OF PATIENT

### 3.1.1. Some features of demography

*** Distribution according to age group**

**Table 3.1. Distribution according to age group**

| **Hospital**<br>**Age group** | **Central Ob-Gyn Hospital n, (%)** | **Tu Du Hospital n, (%)** | **Hospital of Traditional Medicine n, (%)** | **Total n, (%)** |
|---|---|---|---|---|
| < 30 years old | 2 (3.2) | 3 (4.5) | 1 (1.5) | 6 (3.1) |
| 30-34 years old | 6 (9.7) | 11 (16.7) | 10 (14.9) | 27 (13.8) |
| 35-39 years old | 13 (21.0) | 11 (16.7) | 6 (9.0) | 30 (15.4) |
| 40-44 years old | 18 (29.0) | 20 (30.3) | 21 (31.3) | 59 (30.3) |
| 45-49 years old | 21 (33.9) | 15 (22.7) | 19 (28.4) | 55 (28.8) |
| > 49 years old | 2 (3.2) | 6 (9.1) | 10 (14.9) | 18 (9.2) |
| **Total** | **62 (100)** | **66 (100)** | **67 (100)** | **195 (100)** |

The youngest age is 26 and the oldest age is 55. The objects of study are women in the age from 26 to 55 (table 3.1), where 59,1% of patient among studied women has the age from 41 to 49. There are no statistical differences in age in the study among hospitals with p=0,313.

*** Distribution according to occupation:**

**Table 3.2 Distribution according to occupation**

| Hospital Group of occupation | Central Ob-Gyn Hospital n, (%) | Tu Du Hospital n, (%) | Hospital of Traditional Medicine n, (%) | Total n, (%) |
|---|---|---|---|---|
| Cadre | 24 (38.7) | 6 (9.1) | 19 (28.4) | 49 (25.2) |
| Dealer | 6 (9.7) | 11 (16.7) | 8 (11.9) | 25 (12.8) |
| Worker | 8 (12.9) | 11 (16.7) | 5 (7.5) | 24 (12.3) |
| Housewife | 16 (25.8) | 24 (36.4) | 17 (25.4) | 57 (29.2) |
| Rice-grower | 7 (11.3) | 5 (7.6) | 2 (3.0) | 14 (7.2) |
| Other | 1 (1.6) | 9 (13.5) | 16 (23.8) | 26 (13.3) |
| **Total** | **62 (100)** | **66 (100)** | **67 (100)** | **195 (100)** |

The occupation of patients in the studied group mainly is housewife occupying 29,2% and cadre is 25,2%. There are statistical differences in age in the study among hospitals with p=0.003.

*** Education level:**

**Table 3.3 Distribution according to education level**

| Hospital Level | Central Ob-Gyn Hospital n, (%) | Tu Du Hospital n, (%) | Hospital of Traditional Medicinen, (%) | Total n, (%) |
|---|---|---|---|---|
| Primary education | 0 (0) | 10 (15.2) | 13 (19.4) | 23 (11.8) |
| Basic secondary education | 17 (27.4) | 25 (37.9) | 10 (14.9) | 52 (26.7) |
| General secondary education | 18 (29.0) | 22 (33.3) | 19 (28.4) | 59 (30.3) |
| Intermediate level | 6 (9.7) | 3 (4.5) | 9 (13.4) | 18 (9.2) |
| College | 2 (3.2) | 1 (1.5) | 3 (4.5) | 6 (3.1) |

| | | | | |
|---|---|---|---|---|
| University | 16 (25.8) | 5 (7.6) | 11 (16.4) | 32 (16.4) |
| Postgraduate Education | 3 (4.8) | 0 (0) | 2 (3.0) | 5 (2.6) |
| **Total** | **62 (100)** | **66 (100)** | **67 (100)** | **195 (100)** |

The objects of study are in every education level but mainly from basic secondary education upwards, 30.3% has general secondary education, the level of college and university is 19.5%. There are statistical differences in age in the study among hospitals with p=0.002

### 3.1.2. Some features of Ob-Gyn

*** Obstetrical history:**

**Table 3.4 Obstetrical history**

| **History Number of times** | **Pregnancy n, (%)** | **Miscarriage n, (%)** | **Sucking fetus n, (%)** | **To give birth n, (%)** |
|---|---|---|---|---|
| 0 time | 30 (15.4) | 155 (79.5) | 105 (53.9) | 33 (16.9) |
| 1 time | 25 (12.8) | 34 (17.5) | 44 (22.6) | 41 (21.0) |
| 2 times | 36 (18.5) | 3 (1.5) | 28 (14.3) | 84 (43.1) |
| 3 times | 36 (18.5) | 3 (1.5) | 12 (6.2) | 27 (13.9) |
| > 3 times | 68 (34.8) | 0 (0) | 6 (3.0) | 10 (5.1) |
| **Total** | **195 (100)** | **195 (100)** | **195 (100)** | **195 (100)** |

About Ob-Gyn history, there is one unmarried case and other cases are married, 30 cases have not been pregnant and other cases were pregnant and had babies.

*** Gynecological history**

Menstrual nature: The shortest menstrual cycle is 20 days, the longest is 60 days, mainly from 25 to 30 days, The earliest menstrual age is 11 years old (2 patients) and the latest is 21 years old (1 patient). The number of menstrual days mainly is form 3 to 5 days (occupying 84.6%).

**Table 3.5 Menstrual nature**

| Hospital Menstrual nature | Central Ob-Gyn Hospital n, (%) | Tu Du Hospital n, (%) | Hospital of Traditional Medicine n, (%) | Total n, (%) |
|---|---|---|---|---|
| Regular | 52 (83.9) | 58 (87.9) | 46 (68.7) | 156 (80.0) |
| Irregular | 10 (18.1) | 8 (12.1) | 21 (31.3) | 39 (20.0) |
| Total | 62 (100) | 66 (100) | 67 (100) | 195 (100) |

Most patients having regular menstruation occupy 80%

**Table 3.6 To have period pains**

| Hospital To have period pains | Central Ob-Gyn Hospital n, (%) | Tu Du Hospital n, (%) | Hospital of Traditional Medicine n, (%) | Total n, (%) |
|---|---|---|---|---|
| Yes | 38 (61.3) | 31 (47.0) | 26 (38.8) | 95 (48.7) |
| No | 24 (28.7) | 35 (53.0) | 41 (61.2) | 100 (51.3) |
| **Total** | **62 (100)** | **66 (100)** | **67 (100)** | **195 (100)** |

The number of patients having period pains occupies 48.7%, the tumor of uterine smooth muscles can also be a cause of systolic disorder of uterus which results in having period pains, p = 0.036

**Table 3.7 Quantity of menstrual blood**

| Hospital Quantity of menstrual blood | Central Ob-Gyn Hospital n, (%) | Tu Du Hospital n, (%) | Hospital of Traditional Medicine n, (%) | Total n, (%) |
|---|---|---|---|---|
| Little | 23 (37.1) | 22 (33.3) | 20 (29.9) | 65 (33.3) |
| Medium | 33 (53.2) | 39 (59.1) | 33 (49.3) | 105 (53.8) |
| Much | 6 (9.7) | 5 (7.6) | 14 (20.9) | 25 (12.8) |
| **Total** | **62 (100)** | **66 (100)** | **67 (100)** | **195 (100)** |

Every month the quantity of the patient's menstrual blood in the study at a medium level occupies about half and 12.8% has the numerous quantity of menstrual blood and does not have statistical meaning with p=0.17

### 3.1.3. Gynecological history in 3 months before taking medicine

**Table 3.8 Menstrual nature**

| Hospital / Menstrual nature | Central Ob-Gyn Hospital n, (%) | Tu Du Hospital n, (%) | Hospital of Traditional Medicine n, (%) | Total n, (%) |
|---|---|---|---|---|
| Regular | 43 (69.4) | 56 (84.8) | 44 (65.7) | 143 (73.3) |
| Irregular | 19 (30.6) | 10 (15.2) | 23 (34.3) | 52 (26.7) |
| **Total** | **62 (100)** | **66 (100)** | **67 (100)** | **195 (100)** |

Within 3 months before taking part in the study, regular menstrual cycle of patient occupies 73.3% mainly from 25 to 30 days. The number of menstruating days is mainly from 3 to 5 days (occupying 78.9%). About 7% of menstruation has trouble as compared with before (80% of menstruation is in the table 3.5).

**Table 3.9 To have period pains**

| Hospital / Stomachache | Central Ob-Gyn Hospital n, (%) | Tu Du Hospital n, (%) | Hospital of Traditional Medicine n, (%) | Total n, (%) |
|---|---|---|---|---|
| Uncomfortable | 46 (74.2) | 35 (53.0) | 29 (43.3) | 110 (56.4) |
| Unnecessary to take medicine | 3 (4.8) | 8 (12.1) | 2 (3.0) | 13 (6.7) |
| Necessary to take pain-killer | 1 (1.6) | 6 (9.1) | 2 (3.0) | 9 (4.6) |
| Painless | 12 (19.4) | 17 (25.8) | 34 (50.7) | 63 (32.3) |
| **Total** | **62 (100)** | **66 (100)** | **67 (100)** | **195 (100)** |

In the most recent 3 months before taking medicine, a disease having period pains increases 68% as compared with before 48.7%. There are 4.6 % patients necessary to take pain-killer, therefore, need for treatment in these patients is also higher.

**Table 3.10. Quantity of menstrual blood as compared with 3 months before treatment**

| Hospital / Quantity of menstrual blood | Central Ob-Gyn Hospital n, (%) | Tu Du Hospital n, (%) | Hospital of Traditional Medicine n, (%) | Total n, (%) |
|---|---|---|---|---|
| Little | 7 (11.3) | 4 (6.1) | 6 (9.0) | 17 (8.7) |
| Medium | 28 (45.2) | 42 (63.6) | 37 (55.2) | 107 (54.9) |
| Much | 27 (43.5) | 20 (30.3) | 24 (35.8) | 71 (36.4) |
| **Total** | **62 (100)** | **66 (100)** | **67 (100)** | **195 (100)** |

The number of patients which has the numerous quantity of menstrual blood in this period (17%) increases more than before 12.8%, the medium quantity of menstrual blood occupies 54.9%. Specially more as compared with before 3 months of 36.4%, which means sclerotic nucleus increasing menstrual bleeding. There are no statistical differences in age in the study among hospitals with p=0.338

### 3.1.4. Gynecological examination

There is one case of a patient 40 years old (of the hospital of Traditional Medicine in Ho Chi Minh City) who is not married, and has not yet had sex life, so the results of gynecological clinical examination only are 194 cases.

The standard of study is patients who do not catch enclosed the other gynecological diseases, so in gynecological clinic examination, vulva, vagina, cervix, as well as two auxiliary parts are realized as normal.

**Table 3.11 The examination of uterine postures**

| Hospital / Uterine examination | Central Ob-Gyn Hospital n, (%) | Tu Du Hospital n, (%) | Hospital of Traditional Medicine n, (%) | Total n, (%) |
|---|---|---|---|---|
| Intermediate | 5 (8.1) | 3 (4.5) | 2 (3.0) | 10 (5.2) |
| Front way | 36 (58.1) | 42 (63.6) | 51 (77.3) | 129 (66.5) |
| Rear way | 21 (33.9) | 21 (3.8) | 13 (19.7) | 55 (28.4) |

In the group of studying uterus which has the most front way posture of 66.5%, there is no difference in this result among hospitals.

**Table 3.12. Uterine size examination**

| Hospital / Uterine examination | Central Ob-Gyn Hospital n, (%) | Tu Du Hospital n, (%) | Hospital of Traditional Medicine n, (%) | Total n, (%) |
|---|---|---|---|---|
| Normal | 9 (14.5) | 7 (10.6) | 62 (93.9) | 78 (40.0) |
| Large | 53 (85.5) | 59 (89.4) | 4 (6.1) | 116 (60.0) |

The standard of study is patients who have the smallest size of uterine smooth muscles tumor of 2 cm. Therefore, the large size of uterus is common; it can be larger than normal; it can be large equivalent to one month, one month and half, two month fetus. However, the size of uterus has normal limitation in a number of cases. The hospital of traditional medicine in Ho Chi Minh City has about 90% of patients whose the size of uterus does not change, which can be explained because the patients in the study of this establishment have small size of tumor (an average diameter of tumor is 28.3mm)

**Table 3.13. Tumor examination**

| Hospital / Tumor examination | Central Ob-Gyn Hospital n, (%) | Tu Du Hospital n, (%) | Hospital of Traditional Medicine n, (%) | Total n, (%) |
|---|---|---|---|---|
| Clear touch | 55 (88.7) | 17 (25.8) | 2 (3.0) | 74 (38.1) |
| No clear touch | 7 (11.3) | 49 (74.2) | 64 (97.0) | 120 (61.9) |

The cases in which the tumor of uterine smooth muscle is developed towards peritoneum and the large tumor is touchable when examining but small tumors or tumors which are in uterine muscles or developed towards the mucous membrane of uterus are untouchable occupy 61.9%.

### 3.1.5. The result of ultrasound scans on uterine posture

**Table 3.14 The ultrasound of uterine posture.**

| Hospital / Ultra-sound of uterine posture | Central Ob-Gyn Hospital n, (%) | Tu Du Hospital n, (%) | Hospital of Traditional Medicine n, (%) | Total n, (%) |
|---|---|---|---|---|
| Intermediate | 9 (14.5) | 5 (7.6) | 2 (3.0) | 16 (8.2) |

| | | | | |
|---|---|---|---|---|
| Front way | 31 (50.0) | 39 (59.1) | 54 (80.6) | 124 (63.6) |
| Rear way | 22 (35.5) | 22 (33.3) | 11 (16.4) | 55 (28.2) |

Ultrasound of uterine posture accords with the result of clinical examination, mainly 63.6% of the front way of uterine posture. There is no difference among ultrasound times and hospitals with p>0.05.

## 3.2. THE RESULT OF TREATMENT EFFECT OF MEDICINE

### 3.2.1. Menstrual change

**Table 3.15. The quantity of menstrual blood as compared with before treatment**

| **Phase of treatment / Quantity of menstrual blood** | **Phase 1 (%) n=194*** | **Phase 2 (%) n=195** | **Phase 3 (%) n=194*** |
|---|---|---|---|
| Less | 17 (8.8) | 13 (6.7) | 13 (6.7) |
| Similar | 174 (89.7) | 178 (91.3) | 179 (92.3) |
| More | 3 (1.5) | 4 (2.1) | 2 (1.0) |
| **Total** | **194 (100)** | **195 (100)** | **194 (100)** |

* is to lose 01 figure

After treatment the quantity of menstrual blood decreases as compared with before and most of it returns an average level as before the tumor of uterine smooth muscles is discovered (from 54.9% to 92.3%). The number of people having the numerous quantity of menstrual blood in 3 months before treatment also decreases from 36.4% to 1%. However, this result is judged by patients themselves, this is a subjective factor, so it is surely erroneous.

### 3.2.2. Ultrasound scans on the size of the tumor

**Table 3.16 Average size of tumor after treatment**

| Hospital / Average size | Central Ob-Gyn hospital X±SD | Tu Du Hospital X±SD | Hospital of Traditional Medicine X±SD | Common X±SD | p |
|---|---|---|---|---|---|
| Average size L1 | 34.3±7.1 | 41.3±11.0 | 28.3±9.3 | 34.6±10.7 | |
| Average size L2 | 31.1±9.4 | 38.8±11.8 | 27.4±9.2 | 32.4±11.2 | <0.000 |
| Average size L3 | 29.8±9.8 | 39.1±10.9 | 25.7±9.0 | 31.5±11.4 | 0.000 |
| Average size L4 | 28.6±10.2 | 38.3±11.7 | 24.4±9.1 | 30.4±11.9 | 0.000 |

The studied size of tumor of Central Ob-Gyn Hospital averages 34.3mm, Tu Du hospital averages larger size of tumor of 41.3 mm and the hospital Traditional Medicine averages smallest size of tumor of 28.3 mm.

**After taking medicine of phase 1**: As compared with the size of the tumor of uterine smooth muscles in the first time of examination, an average size of tumor is smaller from 34.6 mm to 32.4 mm.

**After taking medicine of phase 2**: The difference in the size of tumor in taking medicine of phase 2 is somewhat clear with the average size of tumor of 31.5 mm.

**After taking medicine of phase 3**: The patients take 630 capsules and come for the final test before terminating study their tumor considerably decreases with the average size of tumor of 30.4 mm, difference before and after treatment has a statistical meaning with $P<0.01$.

**Table 3.17. Average size of tumor from 2 to 4 cm after treatment**

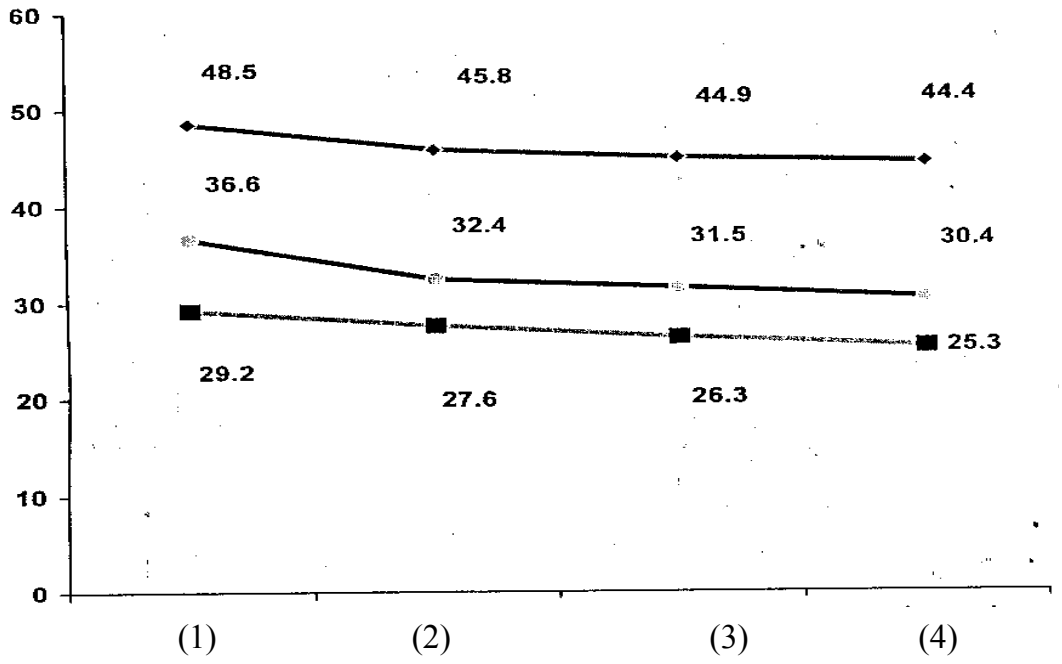
| Hospital / Average size | Central Ob-Gyn hospital n=50 X±SD | Tu Du Hospital n=31 X±SD | Hospital of Traditional Medicine n=59 X±SD | Common n=140 X±SD | p |
|---|---|---|---|---|---|
| Average size L1 | 31.9±5.5 | 31.5±5.7 | 25.6±5.4 | 29.2±6.3 | |
| Average size L2 | 28.8±8.1 | 30.6±6.1 | 24.8±5.3 | 27.5±7.0 | 0.004 |
| Average size L3 | 27.7±9.1 | 30.1±6.2 | 23.1±4.8 | 26.3±7.5 | 0.000 |
| Average size L4 | 26.2±8.7 | 30.5±6.5 | 21.8±4.9 | 25.3±7.6 | 0.000 |

After the first time, the medicine has effect to decrease the tumor average from 29.2 mm to 27.5 mm (decreasing 1.7 mm from the first time to the second time). Decreasing from 27.5 mm to 26.3 mm (decreasing 1.2 mm) from the second time to third time. Before treatment and one month after the termination of treatment, the size of tumor decreases 3.9 mm (from 29.2 mm to 25.3 mm). This difference has a statistical meaning with $p < 0.01$.

**Table 3.18 The Average size of tumor from 4 to 6 cm after treatment**

| Hospital / Average size | Central Ob-Gyn hospital n=12 X±SD | Tu Du Hospital n=35 X±SD | Hospital of Traditional Medicine n=8 X±SD | Common n=55 X±SD | p |
|---|---|---|---|---|---|
| Average size L1 | 44.1±3.2 | 50.0±6.1 | 48.7±5.9 | 48.5±6.0 | |
| Average size L2 | 40.8±8.1 | 47.3±7.7 | 46.8±8.5 | 45.8±8.2 | 0.000 |
| Average size L3 | 38.6±7.4 | 47.1±7.5 | 44.6±10.4 | 44.9±8.5 | 0.000 |
| Average size L4 | 39.9±9.5 | 46.5±7.8 | 43.4±10.4 | 44.4±9.0 | 0.000 |

After the first time the medicine has effect to decrease the tumor with an average size of tumor from 48.5 mm to 45.8 mm (decreasing 3mm). From the second time to the third time, from 45.8 mm to 44.9 mm (decreasing 1 mm) perhaps because the tumor is large the effect of the medicine is weaker. Before treatment and one month after the termination of the treatment, the size of tumor decreases from 48.5 mm to 44.4 mm (4.1 mm). This difference has a statistical meaning with $p < 0.01$.




**(1) Before treatment (2) After the treatment of the first time (3) After the treatment of the second time (4) After the treatment of the third time**

**2-4 cm 4-6 cm 2-6 cm**

**Diagram: 3.1 Change in the size of tumor before and after treatment.**

**Table 3.19 The effect of the tumor treatment**

| Hospital / Treatment effect | | Central Ob-Gyn Hospital n, (%) | Tu Du Hospital n, (%) | Hospital of Traditional Medicine n, (%) | Common n, (%) |
|---|---|---|---|---|---|
| The first time | Very good | 2 (3.2) | 0 (0) | 0 (0) | 2 (1.0) |
| | Good | 12 (19.4) | 6 (9.1) | 3 (4.5) | 21 (10.8) |
| | Moderately good | 13 (21.0) | 13 (19.7) | 11 (16.4) | 37 (19.0) |

| | | | | | |
|---|---|---|---|---|---|
| | To attain | 16 (25.8) | 26 (39.4) | 37 (55.2) | 79 (40.5) |
| | No effect | 19 (30.6) | 21 (31.8) | 16 (29.9) | 56 (28.7) |
| The second time | Very good | 2 (3.2) | 0 (0) | 0 (0) | 2 (1.0) |
| | Good | 18 (29.0) | 7 (10.6) | 12 (17.9) | 37 (19.0) |
| | Moderately good | 15 (24.2) | 14 (21.2) | 19 (28.4) | 48 (24.6) |
| | To attain | 13 (21.0) | 22 (33.3) | 23 (34.3) | 58 (29.7) |
| | No effect | 14 (22.6) | 23 (34.8) | 13 (19.4) | 50 (25.6) |
| The third time | Very good | 6 (9.7) | 1 (1.5) | 0 (0.0) | 7 (3.6) |
| | Good | 18 (29.0) | 8 (12.1) | 24 (35.8) | 50 (25.6) |
| | Moderately good | 8 (12.9) | 14 (21.2) | 16 (23.9) | 38 (19.5) |
| | To attain | 19 (30.6) | 23 (34.8) | 18 (26.9) | 60 (30.8) |
| | No effect | 11 (17.7) | 20 (30.3) | 9 (13.4) | 40 (20.5) |

(Test $X^2$) p1 = 0.013, p2=0.035, p3 = 0.002

+ **Very good result** (The size of tumor decreases as compared with the first instance > 50% of diameter) occupies the ratio of 3.6%.

+ **Good result** (the size of tumor decreases as compared with the first instance from 20%-49% of diameter) occupies the ratio of 25.6%

+ **Moderately good result** (the size of tumor decreases as compared with the first instance from 10%-19% of diameter) occupies the ratio of 19.5%

+ **Attainable result** (not decrease or decrease not over 10%) occupies 30.8%

+ **No effect** (the size of tumor is larger as compared with the first instance) occupies 20.5%

**Therefore, using CRILA capsule to treat the tumor of uterine smooth muscles effectively and decrease the size of tumor reaches the ratio of 79.5%.**

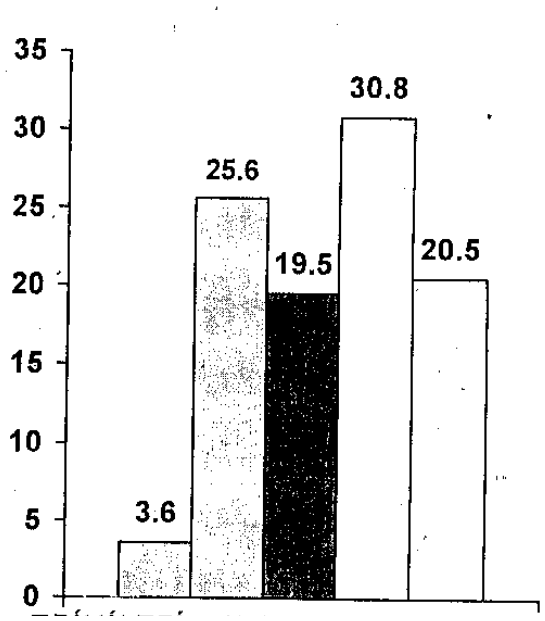



**Diagram 3.2: The treatment effect of common tumor**.

### 3.3. RESULT OF MEDICINE SAFETY

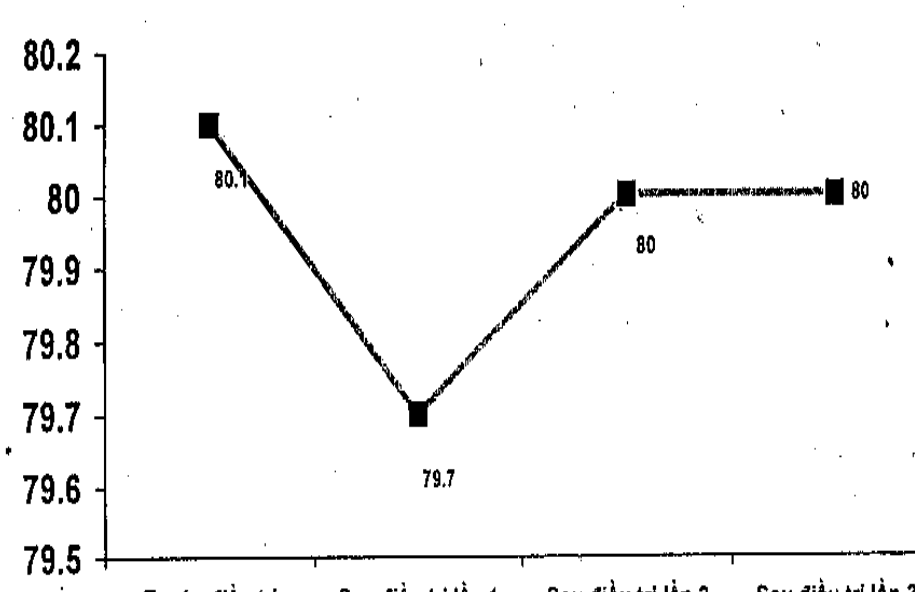
#### 3.3.1 Change in pulse and blood pressure

*** Change in pulse frequency**

**Table 3.20 Change in pulse frequency**

| Hospital / Pulse, Blood pressure | Central Ob-Gyn hospital X±SD | Tu Du Hospital X±SD | Hospital of Traditional Medicine X±SD | Common X±SD | P |
|---|---|---|---|---|---|
| Pulse L1 | 80.3±4.5 | 81.6±4.9 | 78.3±4.5 | 80.1±4.8 | |
| Pulse L2 | 79.6±2.5 | 82.1±4.4 | 77.5±4.9 | 79.7±4.5 | 0.221 |
| Pulse L3 | 80.2±4.5 | 81.8±4.4 | 77.6±4.4 | 80.0±4.8 | 0.336 |
| Pulse L4 | 79.7±4.9 | 81.2±4.2 | 78.4±3.6 | 80.0±4.8 | 0.871 |

Pulse frequencies between the times of taking medicine do not change. As compared with before treatment the average pulse frequencies are 80.1±4.8, they do not also change after treatment (80.0±4.8) with $p > 0.05$




**(1) Before treatment (2) After the treatment of the first time (3)After the treatment of the second time (4) After the treatment of the third time**

**[a] Pulse**

**Diagram: 3.3 Change in the frequencies of heart pulse.**

*** Change in systolic pressure**

**Table 3.21. Change in systolic pressure**

| Hospital / Systolic pressure | Central Ob-Gyn hospital X±SD | Tu Du Hospital X±SD | Hospital of Traditional Medicine X±SD | Common X±SD | p |
|---|---|---|---|---|---|
| Systolic pressure L1 | 113.2±8.8 | 107.1±8.7 | 112.8±9.7 | 111.0±9.5 | |
| Systolic pressure L2 | 113.2±7.3 | 107.1±8.7 | 111.2±14.8 | 110.4±11.1 | 0.351 |
| Systolic pressure L3 | 112.9±5.9 | 107.3±8.5 | 113.0±8.4 | 111.0±8.4 | 1.00 |
| Systolic pressure L4 | 112.3±7.3 | 107.1±8.6 | 112.1±7.1 | 110.5±8.0 | 0.160 |

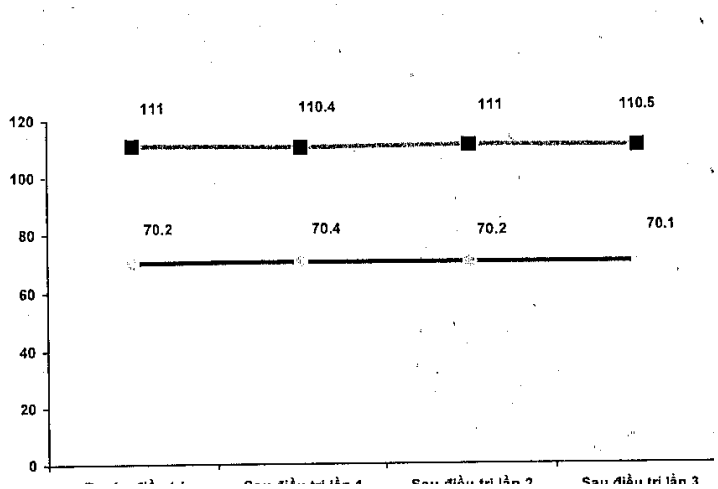
Among treatment times there is no change in systolic pressure as compared with before taking medicine. There is also no considerable change in systolic pressure before (111.0±9.5) and after taking medicine (110.5±8.0) with p > 0.05.

*** Change in diastolic pressure**

**Table 3.22. Change in diastolic pressure**

| Hospital / Diastolic pressure | Central Ob-Gyn hospital X±SD | Tu Du Hospital X±SD | Hospital of Traditional Medicine X±SD | Common X±SD | p |
|---|---|---|---|---|---|
| Diastolic pressure L1 | 72.7±6.3 | 67.1±8.2 | 70.9±7.5 | 70.2±7.7 | |
| Diastolic pressure L2 | 73.4±5.7 | 67.1±8.2 | 70.9±7.3 | 70.4±7.6 | 0.306 |
| Diastolic pressure L3 | 73.4±5.7 | 67.2±8.0 | 70.2±8.1 | 70.2±7.7 | 0.933 |
| Diastolic pressure L4 | 72.6±6.5 | 67.1±8.0 | 70.8±7.2 | 70.1±7.6 | 0.796 |

Diastolic pressure among the times of taking medicine does not change. As compared with before treatment, diastolic pressure (70.2±7.7) does not change as compared with after treatment (70.1±7.6) with p > 0.05.




**(1) Before treatment (2) After the treatment of the first time (3) After the treatment of the second time (4) After the treatment of the third time.**

**■ Systolic pressure — Diastolic pressure**

**Diagram: 3.4 Changes in systolic pressure and diastolic pressure before and after treatment.**

### 3.3.2. Bio-chemical and blood results

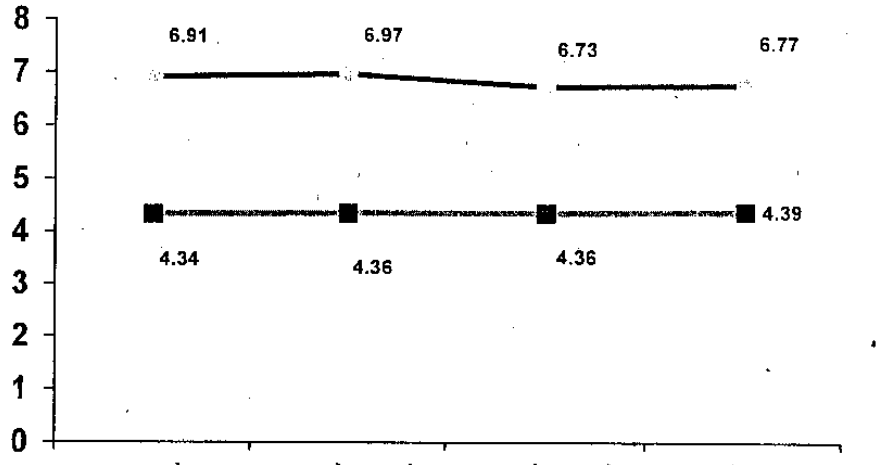
#### 3.3.2.1. The result of hematological test

*** The result of erythrocyte quantity test before and after treatment**

**Table 3.23. Change in erythrocyte before and after treatment**

| Hospital / Erythrocyte | Central Ob-Gyn hospital X±SD | Tu Du Hospital X±SD | Hospital of Traditional Medicine X±SD | Common X±SD | p |
|---|---|---|---|---|---|
| Erythrocyte L1 | 4.28±0.38 | 4.64±0.45 | 4.1±0.32 | 4.34±0.45 | |
| Erythrocyte L2 | 4.24±0.32 | 4.72±0.58 | 4.14±0.38 | 4.36±0.51 | 0.384 |
| Erythrocyte L3 | 4.3±0.44 | 4.65±0.44 | 4.13±0.36 | 4.36±0.47 | 0.488 |
| Erythrocyte L4 | 4.35±0.35 | 4.67±0.57 | 4.16±0.32 | 4.39±0.48 | 0.058 |

The quantity of erythrocyte through the phases of treatment seems to be unchangeable and also similar like this when comparing with before and after treatment. The difference among the phases of taking medicine has no statistical meaning with $p \geq 0.05$




**(1) Before treatment (2) After the treatment of the first time (3) After the treatment of the second time (4) After the treatment of the third time**

■ **Erythrocyte** — **Leukocyte**

**Diagram: 3.5 Changes in erythrocyte and leukocyte**

*** The result of leukocyte quantity test before and after treatment**

**Table 3.24. Changes in the quantity of leukocyte before and after treatment**

| **Hospital** / **Leukocyte** | **Central Ob-Gyn hospital X±SD** | **Tu Du Hospital X±SD** | **Hospital of Traditional Medicine X±SD** | **Common X±SD** | **P** |
|---|---|---|---|---|---|
| Leukocyte L1 | 7.43±1.97 | 7.2±1.6 | 6.16±1.4 | 6.91±1.75 | |
| Leukocyte L2 | 7.5±2.0 | 7.4±2.09 | 6.06±1.4 | 6.97±1.96 | 0.655 |
| Leukocyte L3 | 6.85±2.25 | 7.53±2.03 | 5.85±1.23 | 6.73±2.0 | 0.185 |
| Leukocyte L4 | 7.0±3.87 | 7.0±1.86 | 6.31±1.69 | 6.77±2.63 | 0.447 |

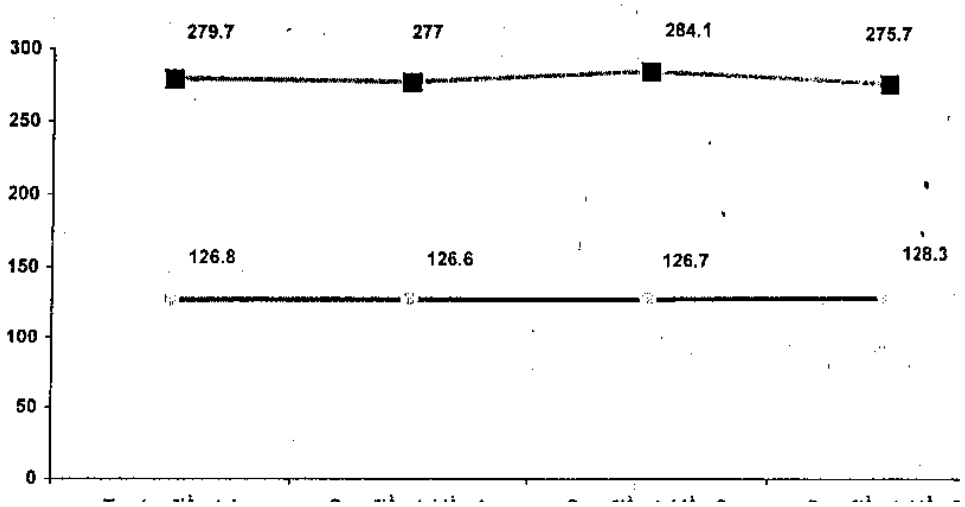
Through the phases of treatment as well as before and after treatment, change in leukocyte index has no statistical meaning with $p > 0.05$.

*** The result of glomerule quantity test before and after treatment**

**Table 3.25. Changes in glomerule indexes among the phases and after treatment**

| Hospital / Glomerule | Central Ob-Gyn hospital X±SD | Tu Du Hospital X±SD | Hospital of Traditional Medicine X±SD | Common X±SD | P |
|---|---|---|---|---|---|
| Glomerule L1 | 261.4±55.6 | 297.3±64.5 | 279.3±57.8 | 279.7±62.4 | |
| Glomerule L2 | 259.5±63.5 | 298.6±67 | 272.0±66.7 | 277.0±67.8 | 0.463 |
| Glomerule L3 | 263.5±56.9 | 299.7±62.0 | 287.9±59.8 | 284.1±61.2 | 0.195 |
| Glomerule L4 | 248.7±50.9 | 293.6±70.3 | 282.9±65 | 275.7±65.3 | 0.300 |

Through the phases of treatment as well as before and after treatment, changes in glomerule indexes have no statistical meaning with $p > 0.05$.




**(1) Before treatment (2) After the treatment of the first time (3)After the treatment of the second time (4) After the treatment of the third time.**

**■ Glomerule — Hemoglobin**

**Diagram 3.6 Changes in glomerule indexes and Hemoglobin**

### 3.3.2.2. The result of Hemoglobin and Hematocrite test

*** Change in Hemoglobin and Hematocrite indexes before and after treatment**

**Table 3.26. Change in Hemoglobin and Hematocrite indexes before and after treatment.**

| Hospital / Glomerule | Central Ob-Gyn hospital X±SD | Tu Du Hospital X±SD | Hospital of Traditional Medicine X±SD | Common X±SD | p |
|---|---|---|---|---|---|
| **Change in Hemoglobin (Hb) g/L** | | | | | |
| Hb L1 | 115.2±14.4 | 128.1±7.2 | 136.2±11.5 | 126.8±14.2 | |
| Hb L2 | 114.2±13.7 | 129.2±9.1 | 135.6±13.0 | 126.6±15.0 | 0.819 |
| Hb L3 | 116.2±15.3 | 129.1±8.3 | 133.7±12.6 | 126.7±14.2 | 0.912 |
| Hb L4 | 122.0±12.3 | 127.2±9.7 | 135.2±12.2 | 128.3±12.6 | 0.089 |
| **Change in Hematocrite (He) %** | | | | | |
| Hematocrite L1 | 0.347±0.044 | 0.387±0.020 | 0.384±0.031 | 0.373±0.037 | |
| He L2 | 0.347±0.037 | 0.389±0.023 | 0.387±0.036 | 0.375±0.038 | 0.434 |
| He L3 | 0.364±0.043 | 0.386±0.025 | 0.384±0.033 | 0.379±0.035 | 0.024 |
| He L4 | 0.375±0.038 | 0.384±0.025 | 0.382±0.031 | 0.380±0.032 | 0.010 |

The result of test shows that there is no change in blood formula such as: quantity of erythrocyte, leukocyte, glomerule, Hemoglobin, Hematocrite of patients joining the study with $p > 0.05$.

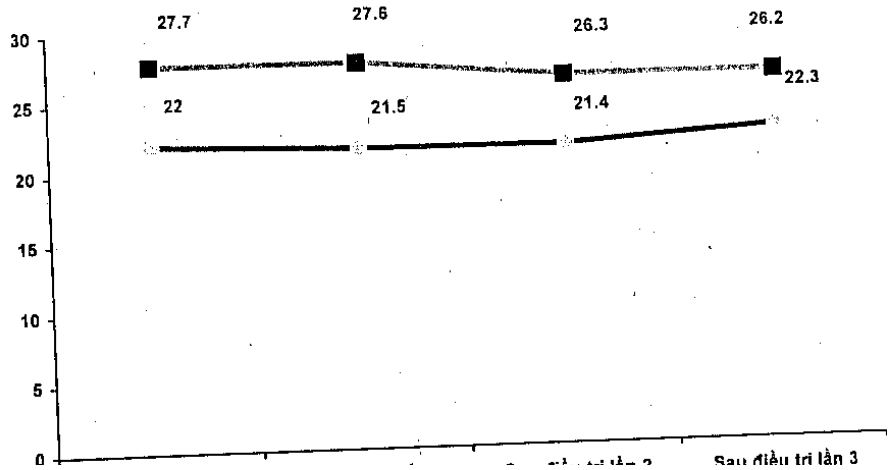
### 3.3.3. The result of biochemical test

#### 3.3.3.1. Change in the function of liver

**Table 3.27. Change in the function of liver is represented by the indexes of SGOT and SGPT among the times of treatment and after treatment**

| Hospital / Index | Central Ob-Gyn hospital X±SD | Tu Du Hospital X±SD | Hospital of Traditional Medicine X±SD | Common X±SD | P |
|---|---|---|---|---|---|
| **Change in SGOT** | | | | | |
| SGOT L1 | 26.2±8.2 | 25.1±8.3 | 31.5±15.1 | 27.7±11.4 | |
| SGOT L2 | 24.8±10.4 | 25.5±6.6 | 32.3±15.7 | 27.6±12.0 | 0.917 |
| SGOT L3 | 23.3±11.5 | 26.3±7.6 | 29.1±13.5 | 26.3±11.3 | 0.200 |
| SGOT L4 | 23.5±7.0 | 25.6±6.5 | 29.4±13.7 | 26.2±10.0 | 0.114 |
| **Change in SGPT** | | | | | |
| SGPT L1 | 18.4±13.4 | 18.8±7.4 | 28.4±15.5 | 22.0±13.4 | |
| SGPT L2 | 17.7±14.3 | 18.2±8.2 | 28.3±16.4 | 21.5±14.2 | 0.656 |
| SGPT L3 | 19.6±18.4 | 19.0±9.2 | 25.5±13.7 | 21.4±14.4 | 0.675 |
| SGPT L4 | 21.6±10.7 | 18.7±10.2 | 26.8±14.0 | 22.3±12.2 | 0.646 |

To evaluate an impact on the function of liver is represented through the indexes of 2 hepatic enzymes which are SGOT and SGPT. Among the times of treatment, change in SGOT and SGPT is not considerable. The concentration of SGOT before treatment is 27.7±11.4 and after treatment is 26.2±10.0 with $p > 0.05$.




**(1) Before treatment (2) After the treatment of the first time**
**(3) After the treatment of the second time (4) After the treatment of the third time.**

**■ SGOT — SGPT**

**Diagram 3.7 Change in hepatic function before and after treatment**

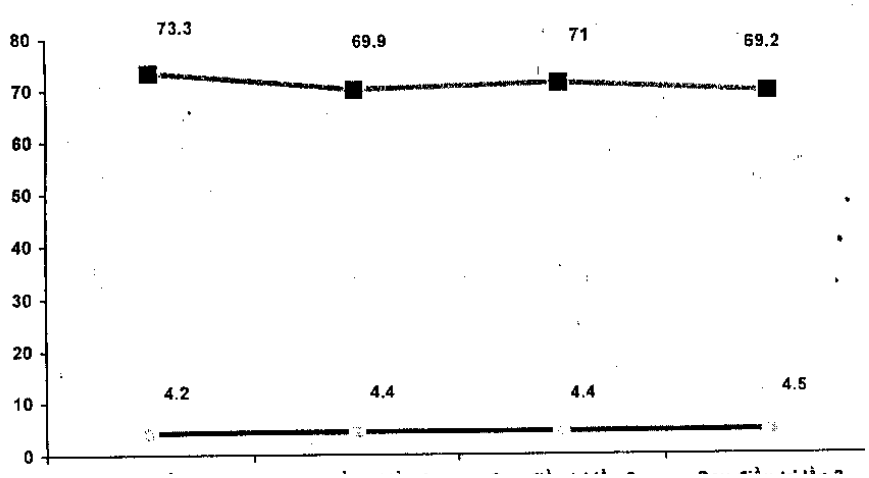
**3.3.3.2. Change in hepatic function**

**Table 3.28. Change in the indexes of Creatinin and Ure among the phases and after treatment.**

| Hospital / Index | Central Ob-Gyn hospital X±SD | Tu Du Hospital X±SD | Hospital of Traditional Medicine X±SD | Common X±SD | p |
|---|---|---|---|---|---|
| **Change in the indexes of Creatinin** | | | | | |
| Creatinin L1 | 75.9±12.9 | 71.5±13.1 | 69.1±16.4 | 73.3±14.4 | |
| Creatinin L2 | 74.8±11.3 | 73.0±9.5 | 62.3±14.8 | 69.9±12.3 | 0.031 |
| Creatinin L3 | 73.4±17.0 | 73.9±10.8 | 66.0±16.4 | 71.0±15.3 | 0.304 |
| Creatinin L4 | 66.9±8.8 | 72.9±12.1 | 67.7±14.8 | 69.2±12.5 | 0.008 |

| **Change in the indexes of Ure** | | | | | |
|---|---|---|---|---|---|
| Ure L1 | 5.4±1.4 | 3.6±0.84 | 3.8±1.2 | 4.2±1.4 | |
| Ure L2 | 5.4±1.2 | 3.9±1.0 | 3.9±1.2 | 4.4±1.4 | 0.031 |
| Ure L3 | 5.6±1.5 | 3.9±1.2 | 3.9±1.2 | 4.4±1.5 | 0.304 |
| Ure L4 | 5.9±1.1 | 3.8±0.84 | 3.9±1.3 | 4.5±1.4 | 0.008 |

The results of surveying renal function after the phases of treatment have average value in normal limitation. The difference among the phases of treatment as well as before and after treatment has no statistical meaning with $p > 0.05$




**(1)Before treatment (2)After the treatment of the first time (3)After the treatment of the second time (4)After the treatment of the third time**

**■ Creatinin — Ure**

**Diagram 3.8: Change in renal function before and after treatment.**

## 3.4. RESULT OF UNDESIRABLE EFFECT

### 3.4.1. Undesirable effects of digestive symptom

**Table 3.29. . Undesirable effects of digestive symptom**

| Treatment time / Side effect | | The first time (n=47,%) | The second time (n=45, %) | The third time (n=31, %) |
|---|---|---|---|---|
| Nausea | Little | 17 (36.2) | 9 (20) | 5 (16.1) |
| | Medium | 2 (4.3) | 0 (0) | 0 (0) |
| | Much | 1 (2.1) | 0 (0) | 0 (0) |
| | No | 27 (57.4) | 36 (80) | 26 (83.9) |
| Vomiting | Little | 3(6.4) | 1 (2.2) | 0 (0) |
| | Medium | 0 (0) | 0 (0) | 0 (0) |
| | Much | 0 (0) | 0 (0) | 0 (0) |
| | No | 44 (93.6) | 44 (97.8) | 31 (100) |
| Diarrhea | Little | 0 (0) | 0 (0) | 0 (0) |
| | Medium | 0 (0) | 0 (0) | 0 (0) |
| | Much | 0 (0) | 0 (0) | 0 (0) |
| | No | 47 (100) | 45 (100) | 31 (100) |

Undesirable effect of digestive symptom is nausea and there is only 9 cases vomiting with mild level, which is not necessary to be intervened. Even the symptom of nausea also decreases gradually after the phases of taking medicine such as the first time there are 17 persons, taking medicine of the second time, 9 persons and the third time, 5 persons. One case at the hospital of traditional medicine when taking 10 capsules at the same time, the patient feel uncomfortable and his/her stomach is irritated, we advise the patients to divide medicine into small doses and take medicine many times in the day, which decreases and loses the symptom of stomach irritation and taking three phases of medicine has good results.

### 3.4.2. Undesirable effects of the symptom of headache, dizziness

**Table 3.30. The side effects of the symptom of headache, dizziness after taking medicine**

| Treatment time / Side effect | | The first time (n=47, %) | The second time (n=45, %) | The third time (n=31, %) |
|---|---|---|---|---|
| Headache | Little | 6 (12.8) | 5 (11.1) | 4 (12.9) |
| | Medium | 6 (12.8) | 5 (11.1) | 4 (12.9) |
| | Much | 2 (4.3) | 1 (2.2) | 1 (3.2) |
| | No | 33 (70.2) | 34 (75.6) | 22 (71.0) |
| Dizziness | Little | 15 (31.9) | 22 (47.8) | 15 (48.4) |
| | Medium | 6 (12.8) | 4 (8.7) | 0 (0) |
| | Much | 5 (10.6) | 2 (4.3) | 2 (6.5) |
| | No | 21 (44.7) | 18 (39.1) | 14 (45.2) |

Generally speaking, the symptoms of headache and dizziness are not considerable and at a mild level, even the concept of "much" is also not considerable because all patients who complain of these effects do not take medicine. On the other hand, a number of patients have disorder manifestations in the period of pre-menopause. They are not the effect of medicine but caused by effects of this period.

### 3.4.3. Undesirable effects of vaginal dryness and hot flush

**Table 3.31. The side effects of vaginal dryness and hot flush after taking medicine**

| Treatment time / Side effect | | The first time (n=47, %) | The second time (n=45, %) | The third time (n=31, %) |
|---|---|---|---|---|
| Vaginal dryness | Little | 4 (8.5) | 6 (13.3) | 3 (9.7) |
| | Medium | 3 (6.4) | 1 (2.2) | 1 (3.2) |
| | Much | 0 (0) | 0 (0) | 0 (0) |
| | No | 40 (85.1) | 38 (84.4) | 27 (87.1) |
| Hot flush | Little | 7 (14.9) | 8 (17.4) | 4 (12.9) |
| | Medium | 5 (10.6 | 3 (6.5) | 2 (6.5) |
| | Much | 1 (2.1) | 2 (4.3) | 1 (3.2) |

| | | | | |
|---|---|---|---|---|
| | No | 34 (72.3) | 33 (71.7) | 24 (77.4) |

**Surveying manifestations after taking medicine among the phases of treatment, the result shows:**

- Side effect of medicine on patients is not considerable: There are not any cases which must treat the side effects of **CRILA** capsule.
- Side effect causing vaginal dryness is cared about by many women but there are only 7 cases in the phase of the first and second treatment and 4 cases in the phase of the third treatment.
- The most common side effect is hot flush, 10 patients complain of this, however, there is only one case which is really uncomfortable.
- From the phase of the second treatment, these undesirable effects decrease gradually; their impact on patient's life is not considerable.

# Chapter 4

# DISCUSSION

## 4.1. DISCUSSION ON COMMON FEATURES OF PATIENT

As a non-control clinical experiment research which is performed at three centres, so homogeneity has a greatly important role because the result is comparison on its own before and after intervention. Therefore, choosing the object of study has been carried out closely at three centres and represented in research design.

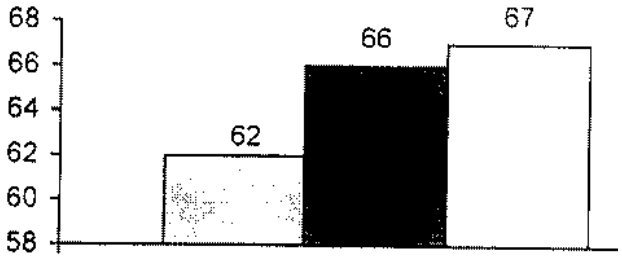
- All of three centres have carried out according to a draft designed in detail with a group of study who are cadres with gynaecology and obstetrics as speciality, and at the hospital of traditional medicine there are also cadres with gynaecology and obstetrics as speciality in traditional medicine.
- Machines and equipment are relatively homogeneous with similar parameters and standards at three hospitals.
- The groups of ultrasound physicians have the unity of process and manipulations defining limitations and the sizes when measuring the nucleus of the tumor of uterine smooth muscles as well as units, weights and measures of the results of bio-chemical and hematological test.
- The quantity of the object of study of 3 centres is 195 patients including:

**+ Central Ob-Gyn hospital: 62**

**+ Tu Du hospital: 66**

**+ The Hospital of Traditional Medicine: 67**

**The number of objects of study at 3 centres**




□ Central Ob-Gyn Hospital ■ Tu Du hospital □ The Hospital of Traditional Medicine

The objects of study with homogeneity are passed with a number of demographic and sociological features.

### 4.1.1. Distribution according to the group of age

The objects of study are women in the ages from 26 to 55 (table 1). The youngest age is 26 and the oldest age is 55. There is 59,1% of patients among the objects of study having the ages from 41 to 49 and 18 patients have the ages from 49 to 55 including: 50 years old: 5 women; 51 years old: 5 women; 52 years old: 3 women; 53 years old: 3 women; 54 years old: 1 woman; and 55 years old: 1 woman. These women‘s menses are still normal, nothing special. Thus in reality there is a group of women in the group of age of pre-menopause having a need for the treatment of the tumor of uterine smooth muscles to feel spiritually secure and at the same time to delay the development of the tumor when they are menopausal. **There is not difference in ages in the study among hospitals with p = 0.313.** As compared with the study of stages 1 and 2, our age of study is more because in reality, the menopause of the some women is late and they have a small tumor and want to treat it.

### 4.1.2. Occupation and learning

The analysis of 179 cases with sufficient figures of occupation (there are 16 cases losing figures), the occupation of patients in the group of study is mainly housewife (occupying 29.2%) and cadres (25.2%).

About education level: The objects of study are in all education levels but mainly from basic secondary education upwards, 30.3% patients has the level of general secondary education, college and university level is 19.5%. Education level, in general, also accords with the study of stages 1 and 2 [4].

### 4.1.3. Ob-Gyn history

About Ob-Gyn history: There is one unmarried case and other cases are married. There are 30 cases which have not yet been pregnant occupying 15.4% but the number of having a miscarriage occupies as many as 79.5%, there can be many patients bearing the consequence of the tumor of uterine smooth muscles which causes difficulties for childbirth. On the other hand, there are 33 cases that have not yet had a child and 41 cases that have one child, therefore, the number of women who has need for childbirth comes to 37.9%. The number of women giving birth two times is 21.3% and three times upwards occupies 61.58%.

The shortest menstrual cycle is 20 days, the longest is 60 days mainly from 25 to 30 days, a number of menstrual cycles are longer from 30 to 35 days. The earliest menstrual age is 11 years old (2 patients) and the latest is 21 years old (1 patient). The number of menstrual days is mainly from 3 to 5 days (occupying 84.6%). Most patients have a regular period (occupying 80%, table 3.5).

The number of patients having period pains occupies 48.7%, the tumor of uterine smooth muscles can also be a cause responsible for systolic disorder of uterus which results in having period pains with $p + 0.036$. The quantity of menstrual blood of monthly menstrual cycles of the patients in the study is at a moderate level and 12.8% has the numerous quantity of menstrual blood but the difference has no statistical meaning because evaluation depends on the subjective judgment of the patients with a large quantity and many centres, incorrectness and non-unity are a natural thing and unavoidable, with $p = 0.17$

### 4.1.4. Ob-gyn history in 3 months before taking medicine and changes after treatment

In 3 months before joining study, regularly menstrual cycles of the patients occupy 73.3% mainly from 25 to 30 days. The number of menstrual days are mainly from 3 to 5 days (occupying 78.9%). About 7% of menstruation is disordered as compared with before (80% of menstruation is in table 3.5)

**The symptom of having period pains:**

In the most recent time, 3 months before taking medicine a disease having period pains increased 68% as compared with before 48.7%; there is 4.6% of patients who needs to take pain-killer. So a need for treatment of these patients is also higher (with $p < 0.01$) The number of patients having the numerous quantity of menstrual

blood in this period is 17% a more increase than before 12.8% but there is no statistical meaning (p = 0.338).

### 4.1.5. Gynecological examination

There is one case of 40 years old (at the Hospital of Traditional Medicine in Ho Chi Minh City) unmarried, no sex life, so only 194 cases have the results of Gynecological clinical examination.

The criteria of study are patients who do not catch other gynecological diseases; therefore, gynecological clinical examination realizes that vulva, vagina, cervix as well as two auxiliary parts are normal.
Standard for patient study is that the size of the smallest tumor of uterine smooth muscles is 2 cm, so it is common to have the large size of uterus. However, there is still some cases of examination, the size of uterus is in a normal limit, because the tumor of uterine smooth muscles can be small, which has not yet change the size of uterus, a sclerotic nucleus under peritoneum does not affect the size of uterus. The number of patients whose the size of uterus does not change is high about 90% at the Hospital of Traditional Medicine in Ho Chi Minh City, this can be explained because patients in the study at this establishment have the small size of the tumor (an average size of tumor is 28.3 mm).

### 4.1.6. Tumor examination

The cases of the tumor of uterine smooth muscles develop towards peritoneum and a large tumor is touchable when examining but small tumors or tumors lying in uterine muscles or developing towards the mucous membrance of uterus are untouchable occupying 61.9%.

## 4.2. DISCUSSION ON TREATMENT EFFECT OF MEDICINE

### 4.2.1. Change in menstruation

After treatment, **CRILA** capsules do not change the menstruation of the patients because menstrual regularity and irregularity depend on regulating mechanism of pituitary gland axis – ovary, we think that with a period of 4 months this mechanism has not yet had effect to regulate irregular menstruation. However, there are changes in the quantity of menstrual blood in menstrual cycles. After treatment, the quantity of menstrual blood decreases as compared with before and most of it returns average level before the tumor of uterine smooth muscles is discovered (from 54.9% up to 93.3%). The number of people having the numerous quantity of menstrual blood in 3 months before treatment decreases from 36.4% to

1%. However, this result is the judgment of the patients; therefore, it is incorrect (table 3.15).

On the other hand, we cannot measure the quantity of lost blood when having a period because this is extremely difficult; therefore, there are special or exact remarks on the quantity of menstrual blood because of depending on the judgment of the patients. But an important remark is that **CRILA** capsules do not cause bleeding in the middle of period, and the effect decreases the symptom of having period pains because the figures disperse and do not have enough reliability, so we do not discuss but will mention it in next study.

### 4.2.2. The size of the tumor before and after treatment

#### 4.2.2.1. The average size of tumor before and after treatment

The size of tumor of Central Ob-Gyn Hospital averages 34.3 mm. Tu Du hospital has the average size of tumor of 41.3 mm and the smallest average size of tumor at the Hospital of Traditional Medicine is 28.3 mm.

***After taking medicine of the first phase:**

That is to say after taking 210 **CRILA** capsules, the patients are invited to come for medical examination and get medicine of a new phase. Comparing with the size of the tumor of uterine smooth muscles in the first time of examination, the average size of the tumor is smaller from 34.6 mm to 32.4 mm.

***After taking medicine of the second phase:**

After taking 210 capsules (phase 1) + 210 capsules (phase 2), the patients are examined again. The difference in the size of the tumor in the phase of taking medicine of the second time shows reduction clearly with the average size of the tumor of 31.5 mm.

***After taking medicine of the third time:**

Patients taking 630 capsules go for the final examination before terminating the study, the tumor decreases considerably with the average size of the tumor of 30.4 mm, the difference before and after treatment has statistical meaning with $p < 0.01$. To evaluate the effect of the medicine on the sizes of different tumors, so we divide the sizes of the tumor into 2 groups from 2-≤ 4 cm and 4-≤ 6cm for analysis.

#### 4.2.2.2. The average size of the tumor from 4 to 6 cm after treatment

After the first and second times, the medicine had an effect to decrease the tumor with the average size of the tumor from 48.5 mm to 45.8 mm (decreasing 3 mm). From the second time to the third time, from 45.8 mm to 44.9 mm (decreasing 1 cm), perhaps because the tumor is large therefore, the effect of the medicine is weaker. Before and after treatment the size of the tumor decreases from 48.5 mm to 44.4 mm (an average decrease is 4.1 mm). This difference has a statistical meaning $p < 0.01$.

#### 4.2.2.3. The average size of the tumor from 4 to 6 cm after treatment

After the first time and second time, the medicine has effect to decrease the tumor with the average size of the tumor from 48.5 mm to 45.8 mm (decreasing 3 mm). From the second time to the third time, from 45.8 mm to 44.9 mm (decreasing 1cm), perhaps because the tumor is large therefore the effect of the medicine is weaker. Before and after treatment, the size of the tumor decreases from 48.5 mm to 44.4 mm (decreasing an average of 4.1 mm). This difference has statistical meaning $p < 0.01$.

Because the standard for choosing sample has the small size of tumor, therefore, in the short time with 3 doses of treatment, a decrease in the size of 1 mm is also valuable, even when the tumor does not develop, which is very encouraging so that patients have a chance of pregnancy or feel secure to wait until menopause or create better conditions for surgery.

Comparing with the study of the first and second stages the effect of decreasing the size of the tumor of uterine smooth muscles of ours is similar and has a statistical meaning. Specially with the study at multi-centre, the size of sample is nearly fourfold as compared with the study of the second stage we think that the results of study are worth recording. Moreover, with the large size of sample, with the distribution according to standard rules therefore, when analyzing generally or particularly the result of decreasing the size of the tumor of **CRILA** capsules has a statistical meaning $p < 0.01$ and ensures reliability.

On the other hand, (there is only one case) when patients eagerly ask for surgery to remove sclerotic nucleus, the tumor is very easy to remove from the layer of sheath.

**4.2.2.4. The effect of tumor treatment**.

+ **Very good result** (the size of the tumor decreases as compared with the first instance > 50% of diameter) occupies the ratio of 3.6%.

+ **Good result** (the size of the tumor decreases as compared with the first instance from 20% - 49% of diameter) occupies the ratio of 25.6%.

+ **Moderately good result** (the size of the tumor decreases as compared with the first instance from 10% - 19% of diameter); the ratio of 19.5%.

+ **Attainable result** (no decrease or decrease not over 10%): 30.8%

+ **No effect** (the size of the tumor is larger as compared with the first instance): 20.5%

**Therefore taking CRILA capsule to treat the tumor of uterine smooth muscles effectively to decreases the size of the tumor reaches the ratio of 79.5%.**

However, there is also 20.5% having no effect that is the tumor increases as compared with before treatment but increase rate is not considerable only a few mm as compared with before treatment. There are not any cases increasing suddenly or having heavy complications which must be intervened for emergency.

The only case of operating to remove sclerotic nucleus is a patient of 29 years old. (Appendix)

Generally speaking, the tumor in all study has a decrease in its size after the phases of treatment, there are cases decreasing the tumor very well right at the first time of treatment phase. However, there are a number cases in which the size of the tumor increases in the treatment process. A patient of 39 years old going for medical examination at Central Ob-Gyp hospital has the size of the tumor of 3cm before treatment, after 3 phases of treatment, the size of the tumor increases 4 cm. And another case a patient, 47 years old, going for medical examination at the Hospital Traditional Medicine of Ho Chi Minh City has the size of the tumor of 2cm before treatment and after treatment its size is 2.5cm. And another case, a patient, 42 years old, going for medical examination at Tu Du hospital has the size of the tumor of 2.1cm before treatment, after treatment its size increases 2.8cm

We realize that the medicine has much effect on small tumors (their diameter is ≤ 6cm) and should be taken continuously because the size of the tumor decreases less in dose 3 as compared with after taking medicine of the first and second times.

## 4.3. DISCUSSION ON THE SAFETY OF MEDICINE IN TREATMENT

### 4.3.1. Change in pulse and blood pressure

*** Change in pulse frequencies**

Pulse frequencies between times of taking medicine do not change. As compared with before treatment, pulse frequency (80.1± 4.8) also does not change after treatment (80.0±4.8) with $p > 0.05$. The study of Tran Duc Tho and Nguyen Khanh Bien when using **CRILA** capsules to treat the enlarged benign prostates of 50 male patients (at the Hospital of Traditional Medicine in Ho Chi Minh City) also does not change pulse frequency when comparing with before, during and after treatment ($p > 0.05$) [9]. Comparing with Tran Thi Loan, the blood pressure is in a normal limitation before and after treating the enlarged benign prostate by **CRILA** capsules for 30 patients at the Viet Nam Institute of Traditional Medicine [11] as well as the result of study of stages 1 and 2 at Central Ob-Gyn Hospital [4].

*** Change in systolic pressure**

Among the times of treatment, there is not change in systolic pressure as compared with before taking medicine. There is also considerable change in systolic pressure before (111.0±9.5) and after taking medicine 9110.5±8.0) with $p > 0.05$. Our remark also accords with Tran Duc Tho and Nguyen Khanh Bien [11], as well as Tran Thi Loan and coworkers [9].

*** Change in diastolic pressure**

Diastolic pressure among the time of taking medicine does not change. As compared with before treatment the value of diastolic pressure (70.2±7.7) does not change as compared with the result of after treatment (70.1±7.6) with $p > 0.05$. The study of Tran Duc Tho and Nguyen Khanh Bien when using **CRILA** capsule to treat the enlarged benign prostate for 50 patients there is not also change in pulse frequency when comparing with before, during and after treatment ($p > 0.05$) and similar as the result of Tran Thi Loan and the study of stages 1 and 2 at Central Ob-Gyn Hospital [4], [9], [11].

### 4.3.2. Change in hematological test

*** The result of erythrocyte indexes test**

The quantity of erythrocyte through the phases of treatment does not seem to change and also similar like this as compared with before and after treatment.

The difference among the phases of taking medicine as well as comparison with before and after treatment does not have statistical meaning with $p \geq 0.05$. When studying the effect on hematological indexes, the study of stages 1 and 2 as well as Tran Duc Tho and Nguyen Khanh Bien, Tran Thi Loan and coworkers also has the same result as ours [4], [9], [11].

*** Change in leukocyte indexes among the phases and after treatment**

Through the phases of treatment as well as before and after treatment, leukocyte indexes do not change considerably and it can be said that there is not change and there is statistical meaning with $p > 0.05$. This remark is also as similar as other authors when studying **CRILA** capsule on people [9], [11] and as compared with the study of stages 1 and 2 it is also the same result as ours [4]

*** Change in the quantity of glomerule before and after treatment**

Through the phases of treatment as well as before and after treatment, glomerule indexes change inconsiderably and it can be said that there is not change and there is statistical meaning with $p > 0.05$. Other authors do not study glomerule so we do not have figures for comparison. Therefore, when using **CRILA** capsules to treat the tumor of uterine smooth muscles the value of glomerule does not change, so it does not affect one of hemostatic factors.

*** Change in the indexes of Hemoglobin and Hematocrite before and after treatment:**

The result of test shows that there is not change in blood formula: the quantity of erythrocyte, leukocyte, glomerule, Hemoglobin, Hematocrite of patients of the study ($p > 0.05$ – table 19, table 20).

### 4.3.3. Bio-chemical result

#### 4.3.3.1. Change in hepatic function

To evaluate the effect on hepatic function is represented by the indexes of 2 hepatic enzymes which are SGOT and SGPT. Among the phases of treatment, the change of SGOT and SGPT is not considerable. Before treatment, SGOT is $27.7 \pm 11.4$ and after treatment $26.2 \pm 10.0$ with $p > 0.05$. Similarly, with the enzyme of SGPT, the change among the phases of treatment as well as before and after treatment, the difference has not statistical meaning with $p > 0.05$. There is only one case, hepatic enzyme increases slightly before and after treatment SGOT is 73 units, the second time, 85 units, the third time, 80 units and after treatment, 80 units; and before treatment SGPT is 63 units, the second time, 77 units, the third time, 75 units and after treatment, 70 units. Patients do

not have any disorder or feel uncomfortable during the process of treatment. Therefore, the medicine does not change the indexes of hepatic function. As compared with the result of study of Tran Duc Tho and Nguyen Khanh Bien as well as the study of Tran Thi Loan and coworkers, the results are the same although the quantity of these authors is less than ours are. Comparing with the study of the effect of **CRILA** capsule on the tumor of uterine smooth muscles at the stages 1 and 2 the results are the same that is **CRILA** capsules do not hurt hepatic function represented by the concentration of SGOT and SGPT.

#### 4.3.3.2. Change in renal function

Change in renal function through the indexes of Creatinin and Ure before and after treatment. The results of surveying renal function (Table 22) after the phases of treatment have average value in a normal limit. The difference among the phases of treatment as well as before and after treatment does not have statistical meaning with $p > 0.05$) therefore, it can be concluded that **CRILA** capsules do not affect hepatic and renal functions of the users. Our conclusions also accord with the results of study of stages 1 and2 [4] as well as other authors [9] [11].

## 4.4. DISCUSSION ON UNDESIRABLE EFFECT

*** Undesirable effects on digestive symptom**

Undesirable effects on digestive symptom are nausea and there are only 9 cases at a mild level. Even nauseous symptom also decreases gradually after the phases of taking medicine such as the first time, 17 persons, the second time, 9 persons, and the third time, 5 persons. There is one case at the Hospital of Traditional Medicine when taking 10 capsules at the same time, the patient's stomach is irritated and he/she feel uncomfortable, we advise the patients to divide the medicine into small doses and taking them many times in the day, which decreases and lose the irritation of the stomach and taking 3 phases of medicine has a good result.

*** Undesirable effects of the symptom of headache, dizziness**.

In general, the symptoms of headache and dizziness are not considerable and mild, even with the concept of "much" is not considerable because all patients who complain of these effects do not need the intervention of medicine. On the other hand, a number patients have disorder manifestations of menopause, so undesirable effects cannot be the effect of the medicine but are caused by menopausal disorder.

*** Undesirable effects of vaginal dryness and hot flush.**

Surveying manifestations after taking medicine between the phases of treatment, the results show:

- Side effect of medicine on patients is not considerable: there is no case in which the side effect of **CRILA** capsules must be treated. The impact of this medicine on digestive tract such as nausea, hot burn in stomach in the first days of taking medicine also decreases gradually and loses all.
- Side effect causing vaginal dryness is cared about by many women but there are only 7 cases at the phases of the first and second treatment and 4 cases at the phase of the fourth treatment. These patients do not need to be intervened with medicine.
- The most common side effect is hot flush, there are about 10 patients compaining of this, however, only one case is really uncomfortable.
- The high acceptance of the medicine can be understood because **CRILA** is traditional medicine, so it is regarded as "benign". Secondly, in reality, taking medicine shows there is not almost any considerable side effect on the users.

However, if patients have the symptom of hot flush, they can use tranquillizers or they are given medical advice carefully so that they can continue to be treated. And patients have vaginal dryness (despite few quantity) they should use ointment to lubricate their vagina to improve this undesirable effect.

# CONCLUSION

**1. CRILA capsule decreases the size of the tumor of uterine smooth muscles effectively:**

- Very good result: the size of the tumor decreases as compared with the first instance > 50% of diameter, occupying the ratio of 3.6%.
- Good result: the size of the tumor decreases as compared with the first instance from 20 % to 49% of diameter or it does not enlarge, occupying the ratio of 25.6%
- Moderately good: the size of the tumor decreases as compared with the first instance from 10% to 19% of diameter, occupying the ratio of 19.5%
- Attainable result: the size of the tumor does not decrease or decrease not over 10%, occupying 30.8%

**+ CRILA capsule treats the tumor of uterine smooth muscles effectively (79.5%)**

**+ CRILA capsule treats the tumor of uterine smooth muscles ineffectively (20.5%)**

**+ The size of the tumor after all of 3 phases of treatment decreases an average from 34.6 mm to 30.4 mm.**

**2. CRILA capsule is safe for users**

- It does not affect pulse, systolic pressure and diastolic pressure
- **CRILA** capsule does not affect hematological indexes such as erythrocyte, leukocyte, and the quantity of glomerule.
- **CRILA** capsule does not affect hepatic and renal functions through the values of hepatic enzymes of SGOT and SGPT as well as the concentration of Creatinin and blood ure.

**3. Undesirable side effects of CRILA**

Occupy 15.9% although the ratio seems to be high, these undesirable effects are nausea, headache, vaginal dryness and hot flush, however, these undesirable effects are often slight and not necessary to intervene.

# RECOMMENDATIONS

- **CRILA** should be used widely to treat the tumor of uterine smooth muscles for the cases of the size of the tumor below 6 cm.
- Extracting high concentration from **CRILA** capsule shoul be studied to help patients use it easily.
- It is necessary to study the effect of **CRILA** on the treatment of the tumor of uterine smooth muscles with the longer time of using medicine.