Thai Journal of Obstetrics and Gynaecology
July 2015, Vol. 23, pp. 165-171

GYNAECOLOGY

Curcumin in Reduction Size of Myoma Uteri

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ABSTRACT

Objective: The objectives of the study were to determine effects of curcumin in decreasing size of leiomyoma and to determine adverse effects of curcumin.

Materials and Methods: The study was a prospective study conducted in reproductive women with leiomyoma in Bhumibol Adulyadej Hospital. 35 women with 81 leiomyoma lumps were recruited to participate by convenience sampling. Ultrasound measurement size of leiomyoma was done before treatment with curcumin. Patients were taken curcumin 1,200 milligrams orally per day for 6 months. Ultrasound measurement size of leiomyoma was repeated at 3 and 6 months after curcumin was started. Main outcomes measure was size of leiomyoma. Size of leiomyoma were compared between before and after taken curcumin for 6 months.

Results: The mean diameter of leiomyoma was statistically different at before and after 3 (4.74 ± 2.78 centimeters VS 4.64 ± 2.75 centimeters) and 6 months (4.74 ± 2.78 centimeters VS 4.46 ± 2.61 centimeters) curcumin intake. And both mean volume of leiomyoma was statistically different at before and after 3 and 6 months curcumin intake. Adverse effect of curcumin was not found.

Conclusions: Curcumin decreased size of myoma uteri after taken 6 months with statistically significant.

Keywords: Curcumin, Leiomyoma, Reduction size

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Introduction

Uterine leiomyoma cause significant morbidity including menorrhagia, pelvic pain, pelvic pressure, infertility, miscarriage and bladder dysfunction[1-9]. The significant symptoms and the progressive nature of the disease frequently require hysterectomy which is associated with surgical morbidity and precludes the opportunity for future childbirth[10].

Myoma uteri are a slow growing disease and usually asymptomatic if the size is not excessively

enlarged. Usually no treatment is needed but it may grow larger. Medications which could reduce the size or even help to keep the size not increasing would be in consideration for prevention of tumor complications and avoiding surgery.

To avoid the risks of surgical intervention, many novel therapies are currently under investigation. An optimal therapy for these tumors would be a medication that has demonstrated efficacy and proven safety.

There are previously reported that leiomyoma is a disease of excessive and dysregulated extracellular matrix (ECM) production[11–12]. There are further hypothesized that leiomyoma may develop from a disorder in wound healing, similar to that seen in keloid formation[11, 13]. The bulk of leiomyoma tumors are made up of ECM. Any effective therapy therefore must regulate both leiomyocyte proliferation and ECM production.

Curcumin has been used for thousands of years as a food additive, and in doses as high as 100 mg/day as a medicine[14]. With regard to regulation of cell proliferation, curcumin act through many signaling pathways to regulate cell growth of various cancers[15]. For example, curcumin suppresses activation of nuclear factor kappa B (NF-kB), activator protein 1 (AP-1), signal transducer and activator of transcription 3 (STAT3) and STAT5, modulates early growth response protein 1 (Egr-1), peroxisome proliferator activated receptor gamma (PPAR-g), b-catenin, and nuclear erythroid 2 p45-related factor 2 (nrf2)[16]. It also down-regulates B-cell lymphoma 2 (Bcl-2), Bcl-XL, cyclooxygenase 2 (COX-2), matrix metalloproteinase 9 (MMP9), tumor necrosis factor (TNF), and cyclin D1[17]. Through these pathways, curcumin inhibits cell proliferation and induces apoptosis in a broad array of abnormal cells.

Curcumin can regulate cell proliferation and fibrosis in various cancers. This compound could have activity in uterine leiomyoma. Curcumin inhibited uterine leiomyoma cell proliferation via regulation of the apoptotic pathway, and inhibited production of the ECM component fibronectin[18]. In vitro curcumin show that the inhibitory effect of curcumin on Eker rat-derived uterine leiomyoma cell (ELT-3 cell) proliferation occurs through the activation of peroxisome proliferator-activated receptor-gamma (PPARg)[19]. In this study, there is hypothesized that curcumin can inhibit growth of leiomyoma cell and then decreased size of leiomyoma.

We review literature of curcumin in treatment of myoma uteri and found 1 study. There was a study from Egypt; they use curcumin 1,350 milligrams per day in treatment of myoma uteri in 12 weeks. The result was both statistically significant decrease in the uterine volume (414.1± 44.3 cubic centimeters VS 201± 33.1 cubic centimeters) and myoma volume (169.8±13.7 cubic centimeters VS 18.7 ± 2.3 cubic centimeters)[20]. Thus we conducted this study to determine effects of curcumin in decreasing size of leiomyoma and to determine adverse effects of curcumin in reproductive age women with leiomyoma in Bhumibol Adulyadej Hospital.

Materials and Methods

This is a prospective study conducted in reproductive age (age 20-55 years old) women with leiomyoma in Bhumibol Adulyadej Hospital. The study was approved by Ethic Committee of Bhumibol Adulyadej Hospital, Directorate of Medical Services Royal Thai Air Force Bangkok, Thailand. The objective of this study is to determine effects of curcumin in decreasing size of leiomyoma and to determine adverse effects of curcumin. The data were collected between June 2012 and March 2014. Women with leiomyoma who attended at Out Patient Department of Bhumibol Adulyadej Hospital were recruited into this study. Inclusion criteria were premenopausal women age 20 – 55 years, asymptomatic or mild symptomatic myoma uteri such as menorrhagia without anemic symptoms that need for blood transfusion, myoma uteri diameter range from 1 to 10 cms. Exclusion criteria were curcumin hypersensitivity, pregnancy, severe symptomatic myoma uteri, adenomyosis and uncontrolled medical conditions.

35 women with 81 leiomyoma lumps were recruited to participate by convenience sampling. After obtaining a written informed consent, all examinations were performed. Size of leiomyoma was a part in inclusion criteria, greatest diameter of leiomyoma

between 1 and 10 centimeters were included in the study. All women who met eligible criteria in the study period were invited to participate. The study was performed in Bhumibol Adulyadej Hospital. This is a tertiary care hospital in Bangkok, Thailand.

Pilot study in 10 cases of myoma uteri with 20 lumps of myoma uteri was done before started the study. Mean difference of myoma uteri before and after receiving curcumin 6 months in pilot study was 0.60. And standard deviation of mean difference was 1.77. Sample size was calculated by using power at 90% and 5% type 1 error at two sides. Calculated sample size was at least 75. In this study, sample size was number of leiomyoma. Because of some patients had more than one of leiomyoma, thus number of leiomyoma were use.

The participants were opposed to receive curcumin 400 milligrams 1 tablet three times a day orally for six months. The curcumin tablet was manufactured by the Government Pharmaceutical Organization of Thailand. No concensus dose for treatment of myoma uteri. Because of lack of any previous in vivo treatment of myoma uteri by curcumin. There was a study from Egypt; they use curcumin 1,350 milligrams per day in treatment of myoma uteri and no any adverse effect. (20) Therefore we use curcumin 1,200 milligram per day in this study because we think it safe for participants. 2D Ultrasound transvaginal and transabdominal measurement was done before treatment, after treatment 3 months and after treatment 6 months. Size, volume and type of myoma were recorded. And mean greatest diameter were collected and calculated for decreasing size of myoma uteri. Mean greatest diameter was calculated by measured 3 dimensions of myoma uteri in centimeters and calculated in mean of 3 dimensions. The ultrasound device was Voluson 730 Pro (GE, Medical system, USA). The operator for ultrasound measurement in all examinations was only single sonographer to avoid inter-observer variability and blind for control information bias. The intra-observer reliability on measuring technique was calculated by 30 randomized myoma uteri in same sonographer. 2D ultrasound was measured twice in each of the 30 myoma uteri. The data in each measurement was assess intra-observer reliability. Size of myoma uteri was measured in 3 dimensions: width, length, and height in centimeters. Volume of myoma uteri was calculated by use formula of sphere's volume in milliliter.

Statistical analysis

All analysis was conducted using the Statistical Package for the Social Sciences (SPSS 16.0, SPSS Inc., USA). Intraclass correlation coefficient (ICCs) was used to examine intra-observer reliability. An ICCs of 1 indicates that all of the observed variances are due to variations between the subjects, whereas an ICCs of 0 indicates that all of observed variances are due to variations within observers[21]. An ICCs > 0.7 is commonly used to indicate sufficient reliability. Normally distributed continuous variables were reported by mean (± standard deviation) and frequencies. The results were analyzed and compared by one-way ANOVA and presented as F and $\alpha = 0.05$ if F > F of $\alpha = 0.05$ was considered statistically significant.

Results

81 myoma uteri lumps (35 participants) were eligible. Two women were excluded due to develop severe symptomatic myoma uteri and needed surgical intervention. Two were excluded due to the change of diagnosis as adenomyosis after 3 months of treatment. One was excluded due to loss of follow up. Two women were excluded due to hormonal usage. Remaining of 69 myoma uteri lumps (28 participants) were included in this study. Mean age of participants was 45.7 year-old. The minimal and maximal numbers of maximal myoma uteri lumps per one participant are 1 and 5 lumps, respectively.

Intra-observer reliability of ultrasonography measurement was studied in 30 myoma uteri. Mean difference was -0.21, standard deviation was 0.33, ICC 0.992, 95% CI 0.984 to 0.996.

Table 1 showed the type of the myoma (categorize by FIGO fibroid classification system)[22]. There was more type5 60.9 percent, type4 36.2 percent. The diameter up to 5 centimeters was 71 percent. After treatment with curcumin, the result was showed as

Table 2. After 3 months, the mean diameter decreased from 4.74 to 4.64 centimeter. Mean Volume from 93.88 to 83.46 cubic centimeters. After 6 months, myoma diameter decrease to 4.46 centimeters and volume decrease to 80.37 cubic centimeters. All the decreasing diameter and volume after 3 and 6 months of receiving curcumin was significant different when compared to before treatment as showed in Table 2. There was no any adverse effects of curcumin found in this study.

Table 1. Characteristic of myoma lumps before treatment

Variables	N (Total myoma uteri = 69 lumps)	%
Type of leiomyoma		
Type 0	0	0
Type 1	1	1.4
Type 2	1	1.4
Type 3	0	0
Type 4	25	36.3
Type 5	42	60.9
Type 6	0	0
Type 7	0	0
Type 8	0	0
Diameter of leiomyoma (Centimeters)		
0-2.0	5	7.2
2.1-4.0	29	42
4.1-6.0	19	27.5
6.1-8.0	6	8.7
8.1-10.0	10	14.5
Volume of leiomyoma (Cubic centimeter)		
0-100	54	78.3
101-200	5	7.2
201-300	3	4.3
301-400	2	2.9
401-500	5	7.2

Table 2. Comparison size and volume of myoma uteri with time

	Before treatment (Mean+SD)	3 mo after treatment (Mean+SD)	F^ (Sig.)	6 mo after treatment (Mean+SD)	F^^ (Sig.)
Diameter (cm.)	4.74±2.78	4.64±2.75	13.20 (0.00)	4.46±2.61	12.63 (0.00)
Volume (cm3)	93.88±167.11	83.46±156.79	255.29 (0.00)	80.37±154.11	201.35 (0.00)

^ - compare before treatment and 3 months after treatment, ^^ - compare before treatment and 3 months after treatment

Discussion

Curcumin decreased both size and volume of 35 from 69 myoma uteri lumps (50.7%) after 6 months taken. At after 3 months of curcumin receiving, diameter and volume decreased 34 from 69 myoma uteri lumps (49.3%). Adverse effect of curcumin was not found.

This study is performed in a single group of participant without concurrent controlled. Leiomyoma uteri are slow progressive disease. All of the cases are asymptomatic. Its changes in size spontaneously within six month period tend to be minimal. Before and after design to answer weather curcumin can reduce size of leiomyoma uteri could be appropriated.

Curcumin can reduce size of leiomyoma by mechanism of inhibits cell proliferation and induces apoptosis in a broad array of abnormal cells such as myoma uteri by many signaling pathways as described in introduction[15,18]. There were no available clinical researches to support this finding.

The result of this study was no different from Ali Farid Mohamed Ali's study[20]. In Ali Farid Mohamed Ali's study both statistically significant decrease in the uterine volume (414.1±44.3 cubic centimeters VS 201± 33.1 cubic centimeters) and myoma volume (169.8±13.7 cubic centimeters VS 18.7±2.3 cubic centimeters) after 12 weeks treatment with curcumin 1,350 milligrams. In this study myoma volume (93.88±167.11VS 80.37±154.11) were also decrease and statistically significant. However, this could not compare because of setting of Ali Farid Mohamed Ali's study different from this study.

Strength of the study were (1) ultrasound measurement method performed by single operator who is an experienced sonographer. (2) Intra-observer reliability (ICCs) were high.

Limitation of the study were (1) limitation of times, we did not perform study in long term use of curcumin and follow up size of myoma uteri after cessation of curcumin. Size of myoma uteri may be larger or same size or smaller as before receives curcumin. (2) Some Confounding factor's control such as hormonal usage not done. But hormonal usage such as Oral contraceptives found no increased risk of fibroid with use or duration of use[23,24]. Studies in women with known fibroids who were prescribed oral contraceptives showed no increase in fibroid growth[25,26]. The new formation of new fibroids does not appear to be influenced by oral contraceptive use[27]. (3) Few previous in vivo study of curcumin in treatment of myoma uteri. That means few studies for comparison with this study. And No concensus dose of curcumin in treatment of myoma uteri.

Curcumin is a diarylheptanoid. It is in one of a popular spice TUMARIC[28]. It may be used as food-coloring. It is easy to find in many countries. It might be the alternative therapy that could be used in patients with asymptomatic uterine leiomyoma. We suggested that further randomized controlled trial studies are needed to be conducted to give us more information concerning efficacy, effectiveness and pharmacology of curcumin. In the further studies are needed to have control group or placebo group for comparison, control confounding factors.

Conclusions

The finding from the study showed curcumin decreased size of myoma uteri after 6 months with statistically significant.

Acknowledgement

We would like to thank Dr. Sinart Prommas, MD. Director of the Department of Obstetrics and Gynecology Bhumibol Adulyadej Hospital. Dr. Paweena Phaliwong MD: Advisor and the staff of the Department of Obstetrics and Gynecology, Bhumibol Adulyadej Hospital, Directorate of Medical Services, Royal Thai Air Force .

References

1. Olufowobi O, Sharif K, Papaionnou S, Neelakantan D, Mohammed H, Afnan M. Are the anticipated benefits of myomectomy achieved in women of reproductive age? A 5-year review of the results at a UK tertiary hospital. J Obstet Gynecol 2004;24:434–40.
2. Salvig JD, Petersen KR, Moller BR. Acute abdominal pain caused by torsion of an enlarged non-pregnant uterus. J Obstet Gynaecol 2005;25:81–2.
3. Sheiner E, Bashiri A, Levy A, Hershkovitz R, Katz M,

Mazor M. Obstetric characteristics and perinatal outcome of pregnancies with uterine leiomyoma. J Reprod Med 2004;49:182–6.
4. Phelan JP. Myomas and pregnancy. Obstet Gynecol Clin North Am 1995;22:801–5.
5. Bulletti C, De Ziegler D, Levi Setti P, Cicinelli E, Polli V, Stefanetti M. Myomas, pregnancy outcome, and in vitro fertilization. Ann NY Acad Sci 2004;1034:84–92.
6. Szamatowicz J, Laudanski T, Bulkszas B, Akerlund M. Fibromyomas and uterine contractions. Acta Obstet Gynecol Scand 1997;76:973–6.
7. Salvador E, Bienstock J, Blakemore KJ, Pressman E. Leiomyoma uteri, genetic amniocentesis, and the risk of second-trimester spontaneous abortion. Am J Obstet Gynecol 2002;186:913–5.
8. Benson CB, Chow JS, Chang-Lee W, Hill JA, Doubilet PM. Outcome of pregnancies in women with uterine leiomyoma identified by sonography in the first trimester. J Clin Ultrasound 2001;29:261–4.
9. Ilbey O, Apaydin E, Gursan A, Cikili N. Bladder leiomyoma: a rare cause of urinary stress incontinence. Arch Ital Urol Androl 2000;72: 85–7.
10. Jacobson GF, Shaber RE, Armstrong MA, Hung YY. Changes in rates of hysterectomy and uterine conserving procedures for treatment of uterine leiomyoma. Am J Obstet Gynecol 2007;196:601.e1–5.
11. Catherino WH, Leppert PC, Stenmark MH, Payson M, Potlog-Nahari C, Nieman LK, et al. Reduced dermatopontin expression is a molecular link between uterine leiomyoma and keloids. Genes Chromosomes Cancer 2004;40:204–17.
12. Leppert PC, Baginski T, Prupas C, Catherino WH, Pletcher S, Segars JH. Comparative ultrastructure of collagen fibrils in uterine leiomyoma and normal myometrium. Fertil Steril 2004;82:1182–7.
13. Leppert PC, Catherino WH, Segars JH. A new hypothesis about the origin of uterine fibroids based on gene expression profiling with microarrays. Am J Obstet Gynecol 2006;195:415–20.
14. Arnon HP, Wahl MA. Pharmacology of Curcuma longa. Planta Med 1991;57:1-7.
15. Shishodia S, Singh T, Chaturvedi MM. Modulation of transcription factors by curcumin. Adv Exp Med Biol 2007; 595:127–48.
16. Aggarwal BB, Kumar A, Bharti AC. Anticancer potential of curcumin: preclinical and clinical studies. Anticancer Research 2003;23:363–98.
17. Shishodia S, Amin HM, Lai R, Aggarwal BB. Curcumin (diferuloylmethane) inhibits constitutive NF-kB activation, induces G1/S arrest, suppresses proliferation, and induces apoptosis in mantle cell lymphoma. Biochem Pharmacol 2005;70:700–13.
18. Malik M, Mendez MD, Paysan M. Curcumin, a nutritional supplement with antineoplastic activity, enhances leiomyoma cell apoptosis and decreases fibronectin expression. Fertil Steril 2009; 91:2177-84.
19. Kenji Tsuiji, Takashi Takeda, Bin Li, Atsuko Wakabayashi, Akiko Kondo, Tadashi Kimura. Inhibitory effect of curcumin on uterine leiomyoma cell proliferation. Gynecological Endocrinology, 2011;27: 512-517.
20. Ali AFM, Ali L. Curcumin a new modality for treatment of uterine myoma. J Am sci, 2013;9:258.
21. Khan KS, Chien PF. Evaluation of a clinical test I: Assessment of reliability. BJOG 2001; 108:562-7
22. Berek J, Berek & Novak's Gynecology fifteenth edition. Lippincott Williams & Wilkins 2012;444-5.
23. Parazzini F, Negri E, La Vecchia C.et al. Oral contraceptive use and risk of uterine fibroids. Obstet Gynecol 1992;79: 430-3.
24. Samadi AR, Lee NC, Flanders WD, Boring JR, 3rd, Parris EB. Risk factors for self-reported uterine fibroids: a case-control study. Am J Public Health 1996;86:858-62
25. Ross RK, Pike MC, Vessey MP, Bull D, Yeates D, Casagrande JT. Risk factors for uterine fibroids: Reduced risk associated with oral contraceptives. BMJ (Clin Res Ed) 1986;293:359–62.
26. Ratner H. Risk factors for uterine fibroids: reduced risk associated with oral contraceptives. BMJ (Clin Res Ed) 1986;293:1027.
27. Orsini G, Larcchia L, Fanelli M. Low-dose combination oral contraceptives use in women with uterine leimoyomas. Minerva Ginecol 2002;54:253-61.
28. Li S, Yuan W, Deng G, Wang P, Yang P, Bharat B. Aggarwal, Chemical Composition and Product Quality Control of Turmeric (Curcuma longa L.). Pharmaceutical Crops 2011;2:28-54.

การศึกษาผลของการใช้ขมิ้นชันในการลดขนาดเนื้องอกมดลูก

อัครพล สุคนธานนท์, ปวีณา ผาลิวงศ์, สินาท พรหมมาศ

วัตถุประสงค์: *เพื่อศึกษาถึงผลของการใช้ขมิ้นชันในการลดขนาดเนื้องอกมดลูก รวมไปถึงผลข้างเคียงจากการใช้ขมิ้นชัน*

วัสดุและวิธีการ: *ทำการศึกษาไปข้างหน้าในกลุ่มคนไข้โรควัยเจริญพันธุ์ที่เป็นโรคเนื้องอกมดลูกในโรงพยาบาลภูมิพลอดุลยเดช โดยคัดเลือกกลุ่มตัวอย่างจำนวน 35 คน ที่มีเนื้องอดมดลูกจำนวน 81 ก้อน ทำการวัดขนาดเนื้องอกมดลูกก่อนการให้ขมิ้นชันโดยใช้เครื่องเสียงความถี่สูง แล้วให้ยาขมิ้นชันในขนาด 1,200 มิลลิกรัมต่อวัน ทางปากเป็นเวลา 6 เดือน และทำการวัดขนาดเนื้องอกมดลูกโดยใช้เครื่องเสียงความถี่สูงซ้ำที่ช่วงเวลาหลังให้ขมิ้นชันที่ระยะเวลา 3, 6 เดือน ตามลำดับ วัตถุประสงค์หลักของการศึกษาคือขนาดเนื้องอกมดลูก เปรียบเทียบขนาดของเนื้องอกมดลูกก่อนและหลังให้ขมิ้นชันเป็นระยะเวลา 6 เดือน*

ผลการศึกษา: *ขนาดเนื้องอกมดลูกเฉลี่ยลดลงอย่างมีนัยสำคัญทางสถิติหลังจากให้ขมิ้นชันเป็นระยะเวลา 3 เดือน (4.74 ± 2.78 เซนติเมตร VS 4.64 ± 2.75 เซนติเมตร) และ 6 เดือน (4.74 ± 2.78 เซนติเมตร VS 4.46 ± 2.61 เซนติเมตร) และปริมาตรเฉลี่ยของเนื้องอกมดลูกลดลงอย่างมีนัยสำคัญทางสถิติหลังจากให้ขมิ้นชันเป็นระยะเวลา 3 และ 6 เดือนเช่นกัน จากการศึกษาไม่พบว่ามีผลข้างเคียงจากการให้ยาขมิ้นชันเกิดขึ้น*

สรุป: *การให้ขมิ้นชันเป็นระยะเวลา 6 เดือนสามารถลดขนาดเนื้องอกมดลูกลงได้อย่างมีนัยสำคัญทางสถิติ*