Fibroid Therapy

G Abd El Fatah, M Elhamamsy, M Abd El Khalek, M Zaki

Citation

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Abstract

Objective: To assess the effect of Amantadine Hcl on the hormonal panel and leiomyoma.Methods: This study was carried out on 29 women receiving 100 mg of Amantadine Hcl orally twice daily for 6 months. All myomas were clinically monitored by ultrasonography as well as determination of estradiol, Follicle Stimulating Hormone [FSH] and Luteinizing Hormone [LH] serum levels statistically by Wilcoxon Signed Rank Test, Ranked Spearman Correlation Test and Chi-square Test. The adverse effects of the drug were monitored.Results: The administration of Amantadine Hcl showed highly significant [$p<0.01$] clinical improvement of symptoms, highly significant [$p<0.01$] reduction in myoma and uterine size, insignificant [$p>0.05$] decrease in FSH and LH levels and highly significant [$p<0.01$] decrease in estradiol level. All adverse effects of the drug were tolerated.Conclusion: Amantadine Hcl improved the therapeutic outcome through relieving symptoms and shrinkage of leiomyoma without any effect on the hormonal panel. More trials are needed.

INTRODUCTION

Leiomyoma is the most common tumor of the female genital tract[1]. Birth control pills probably stimulate fibroid growth[2]. The peripheral conversion of androgen to estrogen by adipose tissue stimulates fibroid growth in obesity[3]. Complications of myoma are atrophy, oedema and menstrual disorders with secondary anemia[4]. Management of fibroid includes myomectomy, uterine artery occlusion, hysterectomy and myolysis. Near menopause radiotherapy may be required. Therapeutic interference includes Gonadotropin-Releasing Hormone analogues[5].

Amantadine hydrochloride capsules have long duration of action[6]. They are indicated for chemoprophylaxis against signs and symptoms of influenza A virus infection[7], the treatment of Parkinsonism and drug-induced extrapyramidal syndromes[8]. The mechanism of action of Amantadine Hcl in the treatment of fibroid is not known. Most probably it has been postulated to cause an acceleration of the well known spontaneous dystrophic phenomena which mark the final stage of the tumor involution[9]. The adverse reactions reported are nausea, insomnia, depression, anxiety, hallucinations, anorexia, dry mouth, ataxia, headache, diarrhea and fatigue[10].

Dystrophic effect induced by Amantadine on uterine myoma was tried successfully in 1982 by Manlio Luisi and Stefano Luisi to avoid surgical and gynecological complications. In other words, medical treatment must be equivalent to myomectomy rather than to hysterectomy. The therapy of Amantadine Hcl in 160 women for 6 months was with good subjective and objective results. Each patient received 200 mg per day orally for 20 days per menstrual cycle. For symptomatic adverse effects, 13 women underwent surgical myomectomy. The postoperative data were confirmed the clinical observations. After 6 months of therapy, the growth of the myomas was stopped and the symptomatology subsided. It is probable that amantadine accelerates the well-known spontaneous dystrophic phenomena which mark the final stage of the vital cycle of the larger and older fibromyomas. In fact, myomas in their intial stages of development, located in the myometrium and still without their own blood supply, maintain full capacity for growth in spite of amantadine and reappear as a recurrence after several years. Therefore, after “chemical myomectomy,” events are similar to that after surgical myomectomy. Fibromas had a tendency to regress spontaneously and supported their hypothesis that amantadine probably acted due to its dopaminergic effect [9].

MATERIALS AND METHODS

The present prospective, pilot self-controlled study was carried out on 50 women, with leiomyoma diagnosed by ultrasonography at Embaba General Hospital, in 2007 to

2009. All the women accepted by their own free will to participate in this study. The patient -based case- control study was selected in this evaluation. They all willingly accepted drug therapy and any necessary surgical interference and signed a consent form for that. The study was approved by an identifiable ethics committee of the hospital, so it was not sent to Institutional Review Board. Women with one or multiple fibroids with normal levels of FSH and LH were included, while menopausal women and women with ovarian disorders were excluded due to their high FSH and LH serum levels, pregnancy as Amantadine Hcl [Adamine from Rameda Company, Cairo Egypt] is contraindicated due to its teratogenic potency, nursing mothers as Amantadine Hcl is excreted in human milk and women with amenorrhea were also excluded due to their low FSH and high LH levels[11]. Each woman received 100 mg Amantadine Hydrochloride capsule twice daily by oral route for 6 months. The compliance with the therapy was assessed by a questionnaire. The women age ranged between 30-51 years with a mean 41.2±6.1 years and the women weight ranged between 58-115 kg with a mean 85.7±14.4 kg.

The obstetric and menstrual history of women was taken. Ultrasonography measured the size of uterus, number, site and size of fibroids before treatment, after 3 months and at the end of therapy. The ovarian graffian follicle growth was monitored by ultrasonography. Determination of serum estradiol level by Competitive ELISA, FSH and LH levels by Sandwich ELISA[12] before treatment, after 3 and 6 months. Adverse effects of Amantadine Hcl were monitored by using questionnaire.

Myoma size= length×width, Uterine size= longitudinal×transverse×anteroposterior diameters and % of reduction in uterine or myoma size= 100×Delta change which is equal to $[Size_{pre}\text{-}Size_{post}] / Size_{pre}$ where $Size_{pre}$ is size before therapy and $Size_{post}$ is size after therapy. Wilcoxon Signed Rank Test used for assessment the significance of changes in myoma, uterine size, FSH, LH, and Estradiol levels after therapy. Ranked Spearman Correlation Test used for determination the correlation of two different parameters. Chi-square Test used for comparison of symptoms before and after therapy.

RESULTS

Of 50 women, 17 were excluded due to emergency surgical indications [severe bleeding or pain]. After 3 months of therapy 3 women were cured and 1 woman became pregnant. A total of 29 women had 42 tumors comprised the population of the study. The most common types of myoma found in the women of the study were 29 intramural myomas [69%], 9 subserous myomas [21.4%] and 4 subendometrial myomas [9.5%] detected by ultrasonography. The obstetric history and menstrual history of women were 6 women [20.7%] had family history of leiomyoma, miscarriage occurred in 8 women [27.5%], 22 women [75.8%] were fertile women, 23 women [79.3%] had dysmenorrhea, 21 women [72.4%] had menstrual discharge and 10 women [34.4%] suffered from presence of blood clots.

The results of clinical examination data demonstrates that before therapy there was 18 women [62.1%] suffered from abdominal pain and after therapy they became 6 women [20.7%] which was highly significant difference [P<0.01]. There was 19 women [65.5%] had menorrhagia before therapy, after therapy there were only 2 women [6.9%] which was highly significant difference [P<0.01]. There was 2 women [6.9%] before therapy had abdominal swelling and no change occurred after therapy which was insignificant difference [P>0.05]. While there was 3 women [10.3%] before therapy had urinary frequency and after therapy they became 1 patient [3.4%] which was insignificant difference [P>0.05].

Before therapy the number of tumors was 42, after 3 months it became 38 tumors and after 6 months it became 36 tumors. The mean of myoma size before therapy was 25.1±30.1cm^2, it decreased to16±26.3cm^2 after three months of therapy and after six months of therapy the mean of myoma size was 15.7±28.6 cm^2 which resulted in 37.4% decrease. Table 1 revealed that there was decrease in the mean of the delta change of myoma size during 3 months of therapy which was highly significant difference [P<0.01]. The mean of the delta change of myoma size after 3 months to after 6 months of therapy decreased which was significant difference [P<0.05] but before therapy to after 6 months of therapy the decrease was highly significant difference [P<0.01]. Before therapy the mean of uterine size was 513.4±383 cm^3, after three months of therapy the mean of uterine size was decreased to 410.4±304 cm^3 and after the end of therapy the mean of uterine size was 335.7±311 cm^3 which resulted in 34.5% decrease. The ovarian Graffian follicles growth was normal. Table 1 revealed that there was decrease in the mean of the delta change of uterine size during 3 months of therapy which was insignificant difference [P>0.05]. The mean of the delta change of uterine size after 3 months to after 6 months of therapy decreased which was significant difference [P<0.05] but before therapy to after 6 months of

therapy the decrease was highly significant difference [P<0.01].

FIGURE LEGENDS

n = Total number of tumors, SD = Standard Deviation, Z = z coefficient

 0-3: Delta change before therapy to after 3 months.

 3-6: Delta change at 3 months to after 6 months of therapy.

 0-6: Delta change before therapy to after 6 months.

- : Decrease in delta change of myoma size or uterine size.

p**< 0.01 [Highly significant], p* < 0.05 [significant] p > 0.05 [insignificant]

Figure 1

Table [1]: The delta change of Myoma size and Uterine size before therapy, after three and six months of therapy [n=42] using Wilcoxon Signed Rank Test

Item	Mean ± SD	Z	*P*
Myoma sizeΔ 0-3 months	-0.05213 ± 1.07287	-2.90411	0.003683**
Myoma sizeΔ 3-6 months	0.833718 ± 4.67751	-2.02296	0.043077*
Myoma size Δ 0-6 months	-0.10478 ± 1.05285	-3.20584	0.001347**
Uterine size Δ 0-3 months	0.042131 ± 0.82293	-1.6758	0.093778
Uterine sizeΔ 3-6 months	0.132263 ± 0.38663	-2.30287	0.021286*
Uterine sizeΔ 0-6 months	-0.21375 ± 0.54017	-3.08131	0.002061**

Before therapy the mean of FSH serum level was 23.6±21 mIU/ml, after three months of therapy it decreased to 20.3±12 mIU/ml and after the therapy it decreased to 16.3±11 mIU/ml. Table 2 revealed that during 3 months of therapy the mean of delta change of FSH level decreased which was insignificant difference [P>0.05]. After 3 months to after 6 months of therapy it decreased which was significant difference [P<0.05] while before therapy to after 6 months of therapy the decrease was insignificant difference [P>0.05]. Before therapy the mean of LH serum level was 15.3±12 mIU/ml, after three months of therapy it increased to 17.2±24 mIU/ml and after therapy it decreased to 12.8±7 mIU/ml. Table 2 revealed that there was decrease in the mean of delta change of LH level during 3 months of therapy, after 3 months to after 6 months of therapy and before therapy to after therapy which was insignificant difference [P>0.05]. Before therapy the mean of estradiol serum level was 106.6±80 pg/ml, after three months of therapy it increased to 117.9±84 pg/ml and after therapy it increased to 232.9±187 pg/ml. Table 2 revealed that during 3 months of therapy the mean of delta change of estradiol level decreased which was insignificant difference [P>0.05]. After 3 months to after 6 months of therapy and before therapy to after 6 months of therapy the decrease was highly significant difference [P<0.01].

FIGURE LEGENDS

n = Total number of women, SD = Standard Deviation, Z = z coefficient

FSH = Follicular stimulating hormone, LH = Lutenizing hormone.

 0-3: Delta change before therapy to after 3 months.

 3-6: Delta change at 3 months to after 6 months of therapy.

 0-6: Delta change before therapy to after 6 months.

- : Decrease in delta change of serum level of FSH or LH or Estradiol

p* < 0.05 [significant] , p > 0.05 [insignificant]. p** < 0.01 [highly significant].

Figure 2

Table[2] : The delta change of serum level of FSH, LH and Estradiol before therapy, after 3 months and after 6 months of therapy among all women using Wilcoxon Signed Rank Test [n=29]

Item	Mean ± SD	Z	*P*
FSH Δ 0-3 months	0.159562 ± 0.58306	-0.20543	0.837239
FSH Δ 3-6 months	0.103165 ± 1.34936	-2.08676	0.03691*
FSH Δ 0-6 months	-0.00582 ± 0.71407	-1.69752	0.089598
LH Δ 0-3 months	0.420965 ± 1.2654	-0.03243	0.974125
LH Δ 3-6 months	1.127485 ± 3.83721	-0.01081	0.991373
LH Δ 0-6 months	0.437759 ± 1.51199	-0.49739	0.618913
Estradiol Δ 0-3 months	1.173526 ± 2.92896	-0.44328	0.657566
Estradiol Δ 3-6 months	1.859846 ± 2.65566	-2.71371	0.006653**
Estradiol Δ 0-6 months	2.479058 ± 3.84152	-3.49215	0.000479**

The total adverse effects of Amantadine Hcl revealed that there were 16 women [55.2%] complained from anxiety, 14 women [48.3%] had nausea and anorexia, 8 women [27.6%] had confusion, 5 women [17.2%] had insomnia, 4 women [13.8%] had dry mouth, 3 women [10.3%] had headache and 2 women [6.9%] had depression. All adverse effects were well tolerated.

Figure 1 revealed that there was negative insignificant correlation between delta change of myoma size after therapy and women age [r=-0.13794].

FIGURE LEGENDS

 : Woman

r : Correlation coefficient

Myoma (B-A) : Delta change of myoma size before therapy to after therapy among all women of the study

Figure 3

Fig.(1): The correlation between delta change of myoma size before to after therapy and age among all women (n=29)

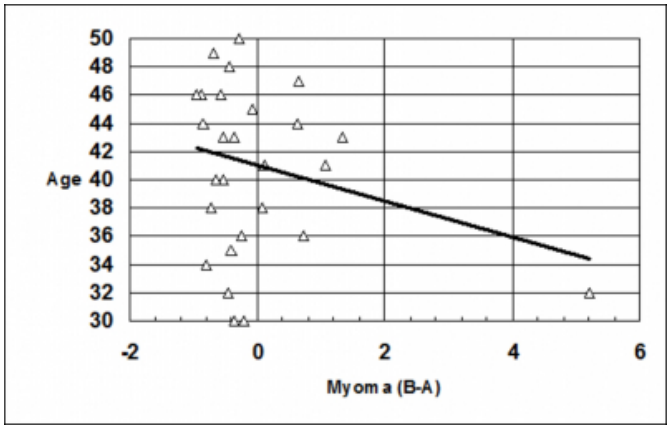


Figure 2 revealed that there was negative insignificant correlation between delta change of myoma size after therapy and myoma size before therapy [r=-0.19349].

FIGURE LEGENDS

Estrogen (B-A) : Delta change of serum level of Estradiol before therapy to after therapy among all women of the study

Figure 4

Fig.(2): The correlation between delta change of myoma size and delta change of Estradiol before to after therapy among all women (n=29)

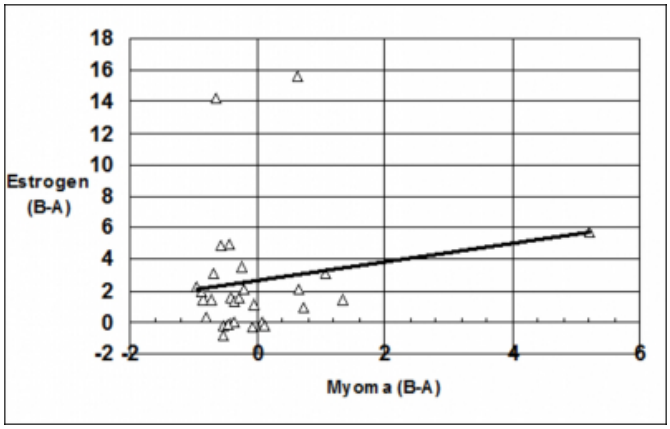


Figure 3 revealed that there was positive insignificant correlation between delta change of myoma size after therapy and delta change of Estradiol level after therapy [r=0.026273].

FIGURE LEGENDS

Uterine size (B-A) : Delta change of uterine size before therapy to after therapy among all women of the study

Figure 5

Fig.(3): The correlation between delta change of myoma size and delta change of uterine size before to after therapy among all women (n=29)

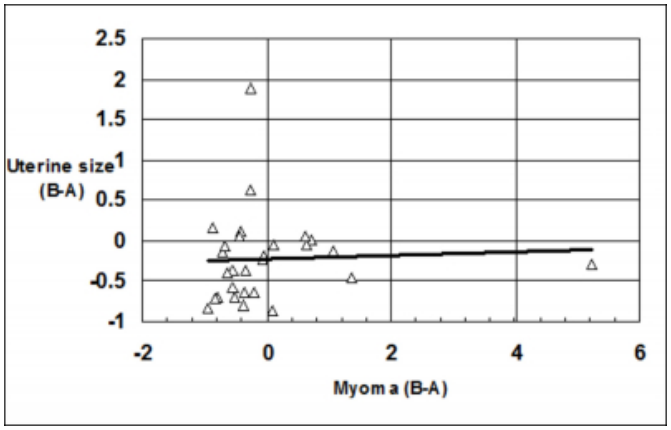


Figure 4 revealed that there was positive insignificant correlation between delta change of myoma size after therapy and delta change of uterine size after therapy [r=0.238643].

FIGURE LEGENDS

Myoma B : Myoma size before therapy among all women of the study

Figure 6

Fig.(4): The correlation between delta change of myoma size before to after therapy and myoma size before therapy among all women (n=29)

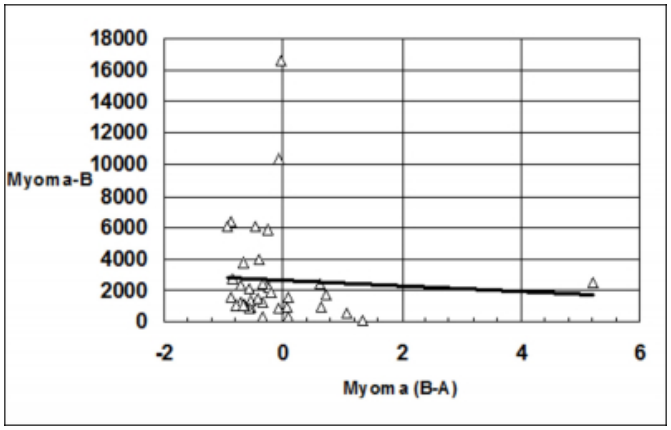


Figure 5 revealed that there was positive insignificant correlation between delta change of myoma size after therapy and Estradiol level before therapy [r=0.089217].

FIGURE LEGENDS

Estrogen B : Serum level of Estradiol before therapy among all women of the study

Figure 7

Fig.(5): The correlation between delta change of myoma size before to after therapy and Estradiol before therapy among all women (n=29)

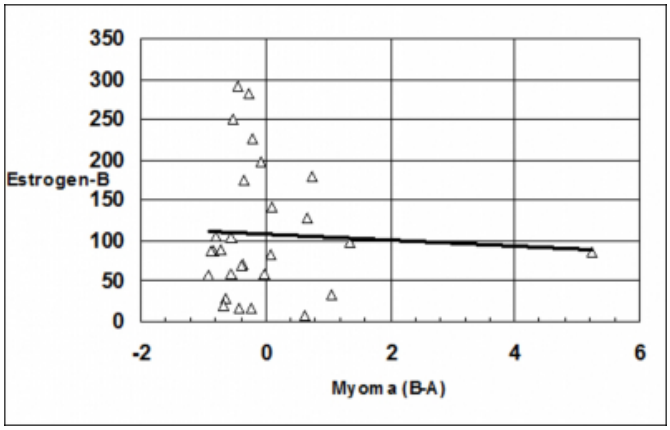


Figure 6 revealed that there was negative insignificant correlation between delta change of myoma size after therapy and uterine size before therapy [r=-0.27617].

FIGURE LEGENDS

Uterine size B : Uterine size before therapy among all women of the study

Figure 8

Fig.(6): The correlation between delta change of myoma size before to after therapy and uterine size before therapy among all women (n=29)

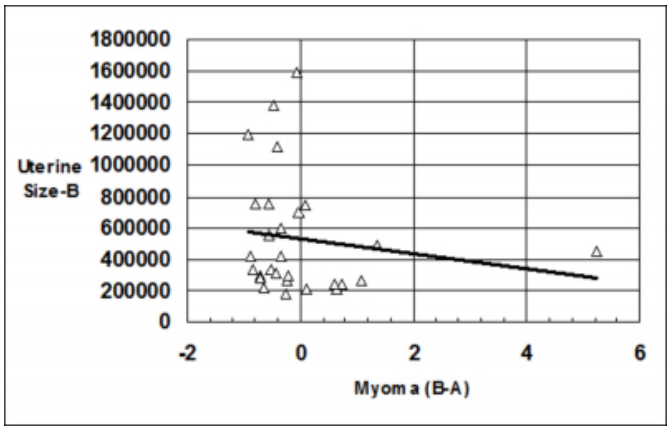


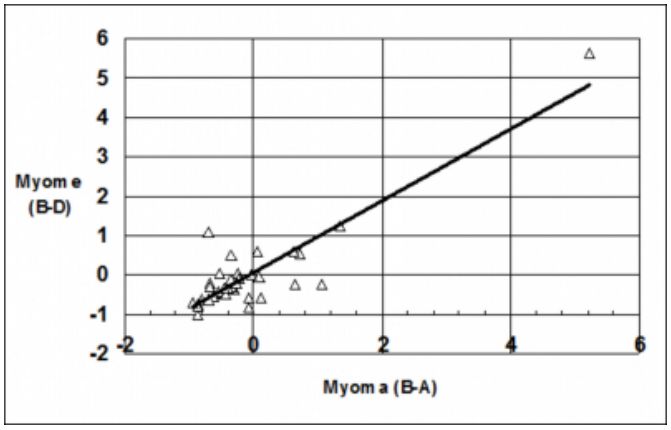
Figure 7 revealed that there was positive highly significant correlation between delta change of myoma size after therapy and delta change of myoma size after three months of therapy [r=0.594337].

FIGURE LEGENDS

Myoma (B-D) : Delta change of myoma size before therapy to after 3 months of therapy among all women of the study

Figure 9

Fig.(7): The correlation between delta change of myoma size before to after therapy and delta change of myoma size before to after three months of therapy among all women (n=29)



DISCUSSION

The therapeutic effect of Amantadine Hcl in pain and menorrhagia may have been partially due to direct inhibition effect on the endometrium as prolonged treatment appears to lower the thickness of the endometrium and pelvic congestion. Luisi and Luisi have reported that after 6 months of therapy growth of the myomas decreased, and the symptomatology subsided[9]. Fillicori et al. and Healy et al. have reported that Amantadine Hcl therapy achieved prompt reduction of the excessive bleeding and relief of pain without the inconvenience of the menopausal symptoms that develop when the Lutenizing Hormone Releasing Hormone analogues were used. Therefore, menorrhagia had decreased when the uterine size decreased which was attributed to Amantadine Hcl therapy[13,14].

The decrease in number of tumors after therapy proved the efficacy of Amantadine Hcl in treatment of myoma. The reduction in myoma size after therapy is similar to that in other report. The histologic appearance of blood vessels within the tumor suggested that the target of the drug was the tumor cells[9]. It is possible to show a reduction in tumor size during therapy. True regressive phenomena appeared after therapy due to its dopaminergic effect[15]. Therefore, an ideal medical treatment must be selective and is effective only on the tumor tropism without change in the normal tissue. It appears that amantadine, a dopaminergic agent not yet used in gynecology will satisfy this requirement[9].

Women with menstrual disorders [amenorrhea or oligomenorrhea in polycystic ovarian syndrome and increased ovarian androgen production particularly testosterone] were excluded which results in high LH levels and low FSH levels that prevent ovulation[16]. Before therapy LH and FSH levels in all women were within the normal levels of the clinical laboratory tests, while estradiol level was elevated. Obese women have higher estrogen levels than those with lower body fat and estrogen are usually present at significantly higher levels in women during the reproductive period[17]. The majority of women were obese [85.7±14.4 kg] and in a reproductive period. This finding demonstrates why estrogen level was elevated before therapy. After 6 months of therapy there was insignificant decrease in FSH and LH levels and highly significant decrease in estradiol level which was attributed to shrinkage of myoma as it is hormonally dependent tumor.

FSH, LH and estradiol levels in this study were taken in the ovulatory phase of the menstrual cycle. The average time of ovulation is the 12th day of 28 day menstrual cycle[18]. The ovulatory phase spans the period of hormonal elevation in the menstrual cycle and this process requires a maximum of 36 hours to complete[19]. So the cycle length differs every menstrual cycle which revealed the difference in FSH, LH and estrogen levels before, during and after therapy.

The clinical monitoring of women receiving Amantadine Hcl revealed that the most common adverse effects were anxiety, nausea and anorexia while the minor side effects were confusion, insomnia, dry mouth, headache and depression which may have been partially due to anticholinergic-like side effects and dopamine central action. These results are similar to that in other report[6]. The most frequently adverse effects of Amantadine Hcl is nausea, while the less frequently reported adverse reactions are depression, anxiety, confusion, anorexia, dry mouth and headache.

There was negative insignificant correlation in this study between the women age and the shrinkage of myoma after 6 months of therapy which was attributed to that the all patients was in reproductive age. Jha et al. have reported that reduction in myoma size was less in older women than in younger women due to decreasing level of female hormones in older women[20].

In this study there was negative insignificant correlation between reduction in estradiol level and the shrinkage of myoma after 6 months of therapy which may be due to polymorphism in COMT gene of the patients. Invitro studies suggest that metabolite 4-OH estradiol may be important in leiomyoma growth. The production of this metabolite is

regulated in part by enzyme catechol -O- methyl transferase [COMT] and its increased activity reduces the level of 4-OH metabolite. COMT gene is polymorphic, 25% of cocusians having a genotype associated with reduced enzyme activity[3]. By Using DNA extracted from peripheral leukocytes of patients, examination of the reduced activity variant was done which is associated with an increased risk of uterine leiomyoma. Therefore, polymorphism in the genes involved in synthesis and metabolism of estradiol is related to leiomyoma.

There was positive insignificant correlation in this study between the reduction in the uterine size and the shrinkage of myoma after 6 months of therapy due to presence of small number of patients in the study. Stewart and Friedman have reported that uterine size decreases 30-64% after 3-6 months of treatment of leiomyoma[21]. Heavy periods are commonly associated with fibroids which enlarge the uterine cavity[3]. Fibroid discomfort may be presented as heaviness in lower abdomen due to the increase in the uterine weight[22]. Taken together, it could be concluded that reduction in uterine size was accompanied by shrinkage of myoma.

In this study there was negative insignificant correlation between the myoma size before therapy and the reduction of myoma size after 6 months of therapy due to presence of small number of patients in the study. It is often easier to treat smaller fibroids than larger ones[21].

In this study, there was positive insignificant correlation between the estradiol level before therapy and the reduction of myoma size after therapy due to presence of obesity in majority of the patients. Jha et al. have reported that estrogen and progesterone-receptor analysis of the treatment revealed there was a substantial correlation between myoma shrinkage and estrogen-receptor content[20].

This study concluded that there was negative insignificant correlation between the uterine size before therapy and the regression of myoma after 6 months of therapy due to absence of uterine anomalies in the patients. In unicornuate Uterus which is one of uterine anomalies, the altered uterine configuration is associated with increase in obstetrical complications e.g. intrauterine fetal growth retardation[23]. This observation may prove a relation between uterine size of anomalies before therapy and efficacy of therapy in myoma shrinkage.

In the present study, 3 women were cured after 3 months of therapy. There was positive highly significant correlation between the reduction of myoma size after 6 months of therapy and the reduction of myoma size after 3 months of therapy. Therefore, the maximum period required to get beneficial results for virgins and nulliparae is 6 months of therapy without any effect on ovulation. Luisi and Luisi have reported a reduction in tumor size during first 3 months of therapy due to reduction of the blood flow[9].

This work did not provide an explanation of the actual mechanism by which Amantadine Hcl favorably alters this improvement. More effort in this field is needed to clarify the mechanism of the action of Amantadine Hcl in uterine leiomyoma. The results in the present work suggest that other safe and effective medical treatment should be developed and it should be insured that their risks and benefits compare favorably with Amantadine Hcl. Continuing studies of Amantadine Hcl will help to define its long-term efficacy and the possible adverse effects. The administration of Amantadine Hcl may provide a valuable managment for women with uterine leiomyoma which needs more clinical trials to confirm its beneficial potentiality.

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Author Information

Gihan Hamdy Abd El Fatah
Imbaba General Hospital Cairo, Egypt

Manal Hamed Elhamamsy, PhD
Assistant Prof. of Clinical Pharmacy, Imbaba General Hospital Cairo, Egypt

Mohammed Samir Abd El Khalek, MD
Head of Obstetrics & Gynecology Department, Imbaba General Hospital Cairo, Egypt

Mammdouh Ahmed Zaki, MD
Prof. of Pharmacology, Imbaba General Hospital Cairo, Egypt