Research Article

Serum Vascular Endothelial Growth Factor Levels and Uterine Fibroid Volume

Hubungan Kadar Serum Vascular Endothelial Growth Factor dengan Volume Mioma Uteri

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Abstract

Objective: To investigate the correlation of serum Vascular Endothelial Growth Factor (VEGF) levels and uterine fibroid volume.

Methods: Observational analytic study was carried out on 80 patients with uterine fibroids indicated myomectomy. Each sample was examined for VEGF levels and volume of myoma tissue post myomectomy was measured by using Archimedes' law. Correlation test using the Spearman test.

Results: A total of 80 samples of patients were examined for VEGF levels and uterine fibroids volume. The median VEGF is 360 pg/mL, the median uterine fibroids volume is 325 ml. The Spearman'stest shows p values (<0.01) and r (0.999).

Conclusions: There is a significant correlation between VEGF levels and uterine fibroids volume. The higher the VEGF level, the greater the volume of uterine fibroids.

Keywords: archimedes law, uterine fibroids volume, VEGF.

Abstrak

Tujuan: *Untuk mencari adanya korelasi antara kadar VEGF terhadap volume mioma uteri.*

Metode: *Penelitian ini berupa analitik observasional. Sampel yaitu pasien dengan mioma uteri yang diindikasikan tindakan miomektomi. Setiap sampel diperiksa kadar VEGF dan pascamiomektomi dilakukan pengukuran volume terhadap jaringan mioma dengan menggunakan hukum Archimedes. Uji korelasi menggunakan Spearman test.*

Hasil: *Sebanyak 80 sampel penderita mioma uteri diperiksa kadar VEGF kemudian dilakukan tindakan miomektomi. Median VEGF adalah 360 pg/mL, median volume uteri adalah 325 ml, uji korelasi Spearman didapatkan nilai p (<0,01) dan r (0,999).*

Kesimpulan: *Terdapat korelasi antara kadar VEGF dengan volume mioma uteri, semakin tinggi kadar VEGF maka semakin besar volume mioma uteri.*

Kata kunci: *hukum Archimedes, VEGF, volume mioma uteri.*

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INTRODUCTION

The knowledge of the mechanisms of growth of uterine fibroids has increased dramatically in recent years. Today, there are numerous potential directions for both the clinician and researcher to proceed when trying to attack these tumours medically.[1] Each tumour appeared to have its own intrinsic growth rate. Tumour size has been related to variation in molecular markers, and it has been assumed that the molecular differences reflect differences in tumour growth rates.[2]

In recent years tumour volume investigations have become a subject of increasing interest.[3] Estimating the size change of an organ is research and clinical assessment that is used to relate symptom development to organ growth, to identify treatment needs, and to evaluate treatment effectiveness.[4]

Vascular Endothelial Growth Factor (VEGF) is the trigger of angiogenesis. VEGF, also known as vascular permeability factor (VPF), is a multifunctional cytokine that increases microvascular permeability and directly stimulates endothelial cell growth and angiogenesis. Vascular endothelial growth factor (VEGF) is synthesized and secreted by various cultured tumour cells and tumours in humans.[5] These observations suggest that VEGF and other proangiogenic factors might be involved in the

development of uterine fibroids.[6]

Measurement of the uterine volume is very important in the follow-up of the treatment response. [7] A range of measurement techniques has been described which may be used to calculate uterine fibroid volume. [8] Archimedes principle can be used as a direct measurement of uterine fibroid volume.[9] Archimedes' principle is one of the most essential laws of physics and fluid mechanics. One of the applications of Archimedes' principle is in the measurement of the density of an irregularly shaped object.[10]

Further experimental studies are required in order to gain a better understanding of the growth factors that are involved in normal and pathological myometrial angiogenesis and to assess the potential of anti-angiogenic treatment strategies for uterine fibroids.[11] Therefore, based on the theories that have been outlined, researchers want to see the correlation of serum levels of Vascular Endothelial Growth Factor (VEGF) with tumorigenesis of uterine myoma which is assessed through the volume of uterine myoma.

METHODS

This is an analytic study with a cross-sectional approach. This study aims to determine the correlation between serum Vascular Endothelial Growth Factor (VEGF) levels and the volume of uterine fibroids. This research was conducted in Obstetrics Gynecology Wards and the Operating Room of the General Hospital Dr. Zainoel Abidin (RSUZA) Banda Aceh from April 2019 to September 2019. Laboratory tests for serum vascular endothelial growth factor (VEGF) levels were conducted at the Prodia Laboratory in Banda Aceh. Measurement of uterine fibroids volume was conducted in the Operating Room.

Inclusion criteria include a diagnosis of uterine fibroids which was proven based on the results of anatomic pathology and patients underwent total myomectomy surgery. Exclusion criteria include tumour metastasis or suffering from other malignancies, pregnancy, menopause, adenomyosis, and being on analogue Gn-RH therapy.

Blood specimens for the examination of VEGF levels were taken from median cubital vein. About 3 ml was inserted into a serum separator tube and sent to the Banda Aceh Prodia Laboratory. The volume of uterine fibroids specimens from myomectomy was measured according to Archimedes' law. A 1000 ml measuring cup is filled with 0.9% NaCl liquid as much as 600 ml (recorded as V1). Cleaned uterine fibroid tissue is dipped into a measuring cup until the entire surface of the uterine fibroids is in the liquid. The increasing volume in the measuring cup is recorded as V2 in ml. Uterine fibroids volume is calculated by the formula V2-V1. Data analysis was performed using the Spearman test. Every numerical data will be tested for normality test.

RESULTS

There were 120 patient with a diagnosis of uterine fibroids in the period of April 2019 to September 2019. A total of 29 were menopause, 2 patients were accompanied by adenomyosis and the remaining 9 were pregnant so were excluded from this study. A total of 80 samples that fit the criteria were conducted anamnesis, physical examination and additional examinations for analysis. All samples were given information and explanations regarding their participation in this study. Ethical eligibility was approved by the Health Research Ethics Committee at the Faculty of Medicine Universitas Syiah Kuala.

General characteristics assessed in this study were age, parity, location of uterine fibroids and patient complaints (Table 1). The independent variable is VEGF levels and the dependent variable is the volume of uterine fibroids.

Ages are grouped based on intervals per 10 years ie 20-29 years, 30-39 years and 40-49 years. Most of the patients in this study were 40-49 years as 67 (83.3%) patients. The mean age in this study was 41.73 ± 4.3 years with a minimum of 26 years to a maximum of 49 years.

The multipara group is the highest frequency in this study as 62 (77.5%) samples. The mean parity in this study was 2.64 ± 1.15.

The most of location uterine fibroids in this study was intramural as 71 (88.8%) samples. The most symptoms that are complained is prolonged menstrual phase (only) as many as 52 (65.0%) samples.

Table 1. General Characteristic

Categoric	Frequency (N=80)	(%)
Age (years)		
20-29	2	2.5
30-39	11	13.8
40-49	67	83.3
Parity		
Nullipara	2	2.5
Primipara	16	20.0
Multipara	62	77.5
Fibroid uterine location		
Intramural	71	88.8
Subserosum	3	3.8
Submucosal	6	7.5
Symptoms		
Prolonged uterine bleeding	52	65.0
Uterus enlargement	2	2.5
Prolonged uterine bleeding and Uterus enlargement	15	18.8
Prolonged uterine bleeding and abdominal pain	11	13.8

The normality test on the VEGF variable shows an abnormal distribution with p-value 0.000 (normally distributed if p> 0.05). After transforming the data using the Log10 function, the p-value obtained still shows that the data are not normally distributed (p = 0.002).

Normality test on variable of uterine fibroid volume shows an abnormal distribution with p-value < 0.001. After transforming the data using the Log10 function, the p-value obtained still shows that the data are not normally distributed (p = 0.002).

The central values and the spread values of the variable VEGF levels and uterine fibroids volume are presented in table 2. The table shows that the median VEGF levels in this study were 360 pg/mL and the median uterine fibroids volume was 325 ml.

Table 2. Median, Minimum and Maximum of VEGF Level and Uterine Fibroids Volume

Parameter	Median	Minimum	Maximum
VEGF	360	82	1528
Uterine fibroids volume	325	70	1390

Because the data distribution of the two variables is not normal, the statistical analysis that can be used to analyze the hypothesis is the Spearman test. The results are presented in Table 3 below.

Table 3. Analysis Results of Spearman's Correlation Test

	Uterine fibroids volume
VEGF level	r = 0.999
	p <0.001
	n = 80

Spearman's correlation test

The Spearman test showed that there was a significant correlation between VEGF levels and uterine fibroid volume with p values <0.001. The r-value of 0.999 shows a positive and strong correlation between the two variables.

DISCUSSION

The prevalence varies, one of them based on the parity, age. Pathologically, the incidence of diagnosed fibroids amplifies gradually with age. At 25-30 years the incidence is only 0.3 per 1000 women-years, but by age 45-50 yearsold, the incidence has raised 20 fold. [9] The frequency of uterine fibroid cases in this study based on age, 20-29 years was 2 (2.5%) samples, 30-39 years was 11 (13.8%) samples and peaked in the 40-49 years was 67 (83.3%) sample. These data indicate that uterine fibroids incidence is increasing by age. The increase in the age of group 40-49 years in this study reached 33-fold compared to the age group 20-29 years.

Most studies conclude that parity is associated with the incidence of uterine fibroids. A woman who has given birth has a lower risk of developing uterine fibroids compared to nulliparous women.[12] Parity was associated with a reduced risk of developing uterine fibroids. In a single-centre study in Japan, the risk of uterine fibroids in women who had given birth three or more times was less than one-fifth that of nulliparous women[13] Although a direct protective effect of pregnancy has been demonstrated, little is known of the mechanism. There have been some suggestions that during postpartum uterine remodelling, there could be selective apoptosis of small lesions. Ischemia during parturition has also been proposed as a mechanism. Thus, it may be implied that fibroid tissue could be highly susceptible to ischemia during both parturition and remodelling.[14]

The highest incidence frequency of uterine fibroids in this study based on parity is the multipara. The increasing incidence of uterine fibroids in the multipara compared to nulliparous

and primiparous was 8-fold and 31-fold, respectively. This result is different from previous studies. The researcher assumes that the sample in this study does not reflect the population in our area so that there are possible differences in results with existing theories.

Uterine myomas have been classified according to their general uterine position: submucous, intramural, and subserosal.[15] Intramural myomas are the most prevalent of all the leiomyomas. Two-dimensional transvaginal sonography detected a 58%–79% occurrence of intramural myomas among study populations with observable myomas.[16] In a multicenter retrospective study involving two-dimensional transvaginal sonography, MRI, and LUS, intramural myomas comprised 58% of all myomas imaged, regardless of the imaging method used.[15] Most of the locations of uterine fibroids in this study are intramurally followed by submucosal and subserosal.

Presenting symptoms play an important role in deciding the appropriate form of treatment for the affected woman. Management strategies are usually individualized based on the severity of the symptoms, the size and location of the fibroid, the patient's age and their chronological proximity to menopause, and the patient's desire for future fertility[12]

The majority of women with uterine fibroids are asymptomatic, and consequently get less clinical attention; fibroid tumours often remain undiagnosed. The most common presenting factor that symptomatic women typically complain about is abnormal uterine bleeding, specifically in terms of heavy and prolonged bleeding.[12] The main complaint in this study is similar to existing epidemiological data. Prolonged menstrual phase complaints are the most common complaints in cases of uterine fibroids.

Correlation of VEGF Levels to Uterine Fibroids Volume

Theoretically, fibroid tumours generally grow slowly. In addition, the rate of growth of uterine fibroid in a patient also varies and some tumours will even spontaneously regress during growth. Therefore, it will be very difficult to predict the growth of uterine myomas or the onset of symptoms.[2]

Fibroid volume is one of important parameter for choosing the management options from no need any intervention as in small asymptomatic myomas, to surgical intervention in symptomatic one or cases of the large uterus with myomas comparable to or in surplus of 12-14 week pregnancy. Uterine fibroid volume is also necessary in follow up of cases under medical treatment (e.g Gn-RH analogues) to assess its success, while in cases of rapid growth planned for surgical intervention, myoma volume helps us to decide the incision type, site and length to diminish the surgical complications.[9]

Growth factors are involved in the pathogenesis of uterine fibroid by regulation of angiogenesis, which is necessary for the growth of uterine fibroid. Angiogenesis is a system that is controlled by proangiogenic and antiangiogenic factors.[6,17] One of the important factor in angiogenesis is vascular endothelial growth factor (VEGF).[18] Several authors report that VEGF plays an important role in stimulating tumour growth.[19] VEGF has a mitogenic effect on endothelial cells that cause cell proliferation. VEGF also influences endothelial cell survival by inhibiting apoptosis.[2]

Spearman's correlation analysis in this study shows that there is a correlation between VEGF levels and the volume of uterine fibroids. The correlation between these two variables is very strong ($r=0.999$) with the direction of a positive correlation which means that the higher the level of VEGF, the greater the volume of myoma fibroids regardless of other factors that make biased.

VEGF is a potent proangiogenic factor and is an essential growth factor for vascular endothelial cells. The development of leiomyoma is associated with exposure to ovarian sex steroids and an increased requirement for vascular supply for their growth. These observations suggest that VEGF and other proangiogenic factors might be involved in the development of leiomyomas.[6]

The contribution of VEGF to tumour angiogenesis is well understood. VEGF is up-regulated in many tumours and VEGF protein was detected in the culture media from a range of tumour cell lines. VEGF mRNA was also detected in numerous tumours and metastases, with immune reactivity for VEGF localized on tumour cells and in the stromal matrix. VEGF might be released

into the surrounding stromal matrix, which might contribute to tumour growth and metastasis in a paracrine manner through angiogenesis and increased vascular permeability. These findings suggested VEGF may promote tumour growth by direct pro-survival effects in tumour cells.[6]

CONCLUSION

The median VEGF and median volume of uterine fibroids in this study were 360 pg/mL and 325 ml, respectively. There is a significant correlation between VEGF levels and uterine fibroids volume. The higher the VEGF level, the greater the volume of uterine fibroids.

SUGGESTION

Hopefully, this research can be continued to find a VEGF cut off point to detect a beginning of progressive growth rate of uterine fibroids in a larger sample.

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