

DOI: <https://doi.org/10.17816/JOWD71087>

An experiment of using the SonoVue ultrasound contrast agent for focused high-intensity ultrasound ablation of uterine fibroids

© Ekaterina A. Slabozhankina¹, Evgeniy F. Kira¹, Alla K. Politova¹, Vyacheslav M. Kitayev¹, Sergej V. Bruslik¹, Yulia L. Amelina¹, Aleksandra A. Politova²

¹ National Medical and Surgical Center named after N.I. Pirogov, Moscow, Russia;

² I.M. Sechenov First Moscow State Medical University (Sechenovskiy University), Moscow, Russia

BACKGROUND: One of the modern methods of organ-saving non-invasive remote treatment of uterine fibroids is ablation of myomatous nodes with high-intensity focused ultrasound (HIFU).

AIM: The aim of this study was to analyze changes in the parameters of ultrasonic ablation when using intraoperative control with the help of an *ultrasound contrast agent*.

MATERIALS AND METHODS: In the period from 2016 to 2018, a total of 208 patients with symptomatic uterine myoma underwent HIFU ablation of myomatous nodes. The two groups of patients were compared: group I included 98 patients aged 36 to 52 years (mean age: 44.39 ± 7.12 years) with intraoperative control with an ultrasound contrast agent (sulfur hexafluoride); group II consisted of 110 patients aged 20 to 55 years (mean age: 38.33 ± 8.72 years), whose treatment was not controlled by the contrast agent.

RESULTS: Using the Mann-Whitney test, we obtained statistically significant differences in the following parameters: the duration of ultrasound ablation was 215.28 ± 70.57 min (from 70 to 390 min) in group I, and 610.84 ± 56.26 min (from 290 to 1230 min) in group II ($p < 0.005$); the average energy was 329.06 ± 33.06 W in group I, and 293.68 ± 64.51 W in group II ($p < 0.001$); good tolerance of the operation was shown in 91% of cases in group I, and in 61.8% of cases in group II; satisfactory tolerance of the operation was shown in 7.7% of cases in group I, and in 37.3% of cases in group II ($p < 0.001$).

CONCLUSIONS: The data obtained indicate that the performance of HIFU ablation with the use of an ultrasonic contrast agent allowed halving the insonation time, while using submaximal and maximum ultrasound exposure powers with better tolerance of intervention by patients.

Keywords: uterine fibroids; high-intensity focused ultrasound ablation; ultrasound contrast.

To cite this article:

Slabozhankina EA, Kira EF, Politova AK, Kitayev VM, Bruslik SV, Amelina YuL, Politova AA. An experiment of using the SonoVue ultrasound contrast agent for focused high-intensity ultrasound ablation of uterine fibroids. *Journal of Obstetrics and Women's Diseases*. 2021;70(2):77–82. DOI: <https://doi.org/10.17816/JOWD71087>

УДК 618.14-006.36-08

DOI: <https://doi.org/10.17816/JOWD71087>

Применение контрастного препарата гексафторид серы (SF_6) при абляции миоматозных узлов фокусированным ультразвуком высокой интенсивности

© Е.А. Слабожанкина¹, Е.Ф. Кира¹, А.К. Политова¹, В.М. Китаев¹, С.В. Бруслик¹, Ю.Л. Амелина¹, А.А. Политова²

¹ Национальный медико-хирургический Центр им. Н.И. Пирогова, Москва, Россия;

² Первый Московский государственный медицинский университет им. И.М. Сеченова (Сеченовский университет), Москва, Россия

Обоснование. Одним из современных методов органосберегающего неинвазивного дистанционного лечения миомы матки является абляция миоматозных узлов фокусированным ультразвуком высокой интенсивности.

Цель — проанализировать изменения параметров ультразвуковой абляции при применении интраоперационного контроля с помощью ультразвукового контрастного вещества.

Материалы и методы. В период с 2016 по 2018 г. 208 пациенткам с симптомной миомой матки выполнена абляция миоматозных узлов фокусированным ультразвуком высокой интенсивности. Определены две группы больных. В первую включены 98 пациенток в возрасте от 36 до 52 лет (в среднем — $44,39 \pm 7,12$ года) с интраоперационным контролем при помощи ультразвукового контрастного вещества гексафторид серы (SF_6). Вторую группу составили 110 больных в возрасте от 20 до 55 лет (в среднем — $38,33 \pm 8,72$ года), лечение которых не контролировали контрастным препаратом.

Результаты. Были получены статистически достоверные (с применением критерия Манна – Уитни) различия в двух группах по следующим параметрам: продолжительность ультразвуковой абляции в первой группе составила $215,28 \pm 70,57$ мин (от 70 до 390 мин), во второй группе — $610,84 \pm 56,26$ мин (от 290 до 1230 мин, $p < 0,005$); усредненная энергия в первой группе — $329,06 \pm 33,06$ Вт, во второй группе — $293,68 \pm 64,51$ Вт ($p < 0,001$); хорошая переносимость операции отмечена в первой группе в 91 % наблюдений, во второй группе — в 61,8 %; удовлетворительная переносимость операции в первой группе составила 7,7 %, во второй группе — 37,3 % соответственно ($p < 0,001$).

Выводы. Полученные результаты свидетельствуют, что выполнение абляции фокусированным ультразвуком высокой интенсивности с применением ультразвукового контрастного препарата позволило в два раза уменьшить время инсонации, использовать субмаксимальные и максимальные мощности ультразвукового воздействия при лучшей переносимости вмешательства.

Ключевые слова: миома матки; абляция фокусированным ультразвуком высокой интенсивности; ультразвуковой контраст.

Как цитировать:

Слабожанкина Е.А., Кира Е.Ф., Политова А.К., Китаев В.М., Бруслик С.В., Амелина Ю.Л., Политова А.А. Применение контрастного препарата гексафторид серы (SF_6) при абляции миоматозных узлов фокусированным ультразвуком высокой интенсивности // Журнал акушерства и женских болезней. 2021. Т. 70. № 2. С. 77–82. DOI: <https://doi.org/10.17816/JOWD71087>

BACKGROUND

Ablation of myomatous nodes by high-intensity focused ultrasound (HIFU) is a modern treatment method for uterine fibroids [1–3]. It provides noninvasive and remote action on myomatous nodes by creating hyperthermic areas in the focusing zone of ultrasonic waves, inducing coagulative necrosis of myoma tissues. When performing this type of intervention, the diagnostic ultrasound is used for intraoperative control in real time, while the controlling ultrasound transducer is rigidly connected to the therapeutic lens of the device. New technologies, currently used in diagnostic ultrasound research, introduced ultrasound contrasting into the clinical practice of ultrasound ablation, a highly effective and informative method of intraoperative control.

Since 2008, in the N.I. Pirogov National Medical and Surgical Center, the HIFU method is used for the treatment of benign and malignant tumors in parenchymal organs of various locations, including uterine fibroids [4, 5]. The technology and equipment were developed in China (Model JC Focused Ultrasound Therapeutic System) by Chongqing HAIFU Technology Company and are registered by the Russian Federal Service for Surveillance in Healthcare. According to the literature, the HIFU ablation technology has several advantages over other methods in treating patients with uterine fibroids — it is a noninvasive and organ-preserving method, does not have a clinically significant general effect on the body, and is not accompanied by a long period of rehabilitation and temporary disability, which is generally positively reflected on the quality of life of patients [6, 7].

For better control and visualization when performing ablation of myomatous nodes with HIFU, our center uses one of the most modern ultrasound contrast agents, sulfur hexafluoride (SF_6 , SonoVue) [8], registered and approved for use in the Russian Federation. The drug represents a suspension of microbubbles (2.5 μm in diameter) surrounded by an elastic membrane of phospholipids. The microbubbles are filled with an inert gas with a low level of solubility in water, which, when it enters the blood, remains inside the microbubbles but diffuses through the membranes of the lung alveoli and is released with exhaled air. That is why a high stability of microbubbles in the bloodstream is ensured, along with rapid excretion through the pulmonary capillaries. Fifteen minutes after the injection of an ultrasound contrast agent, the entire volume of gas administered is eliminated with the exhaled air. The substance injected circulates exclusively in the vessels. This distinguishes it from X-ray contrast agents and paramagnetic substances, which are distributed throughout the intercellular fluid [9–12].

This study aimed to analyze the changes in various parameters of ultrasound ablation, when using intraoperative control with the use of an ultrasound contrast agent, and assess the tolerance to the surgery of patients.

MATERIALS AND METHODS

HIFU ultrasound ablation was performed in 208 patients with symptomatic uterine fibroids, between 2016 and 2018. The patients were divided into two representative groups. Group 1 (study) included 98 female patients, aged 36–52 years (mean age 44.39 ± 7.12 years), with intraoperative control using an ultrasound contrast agent (SF_6) before the onset of HIFU ablation and after the end of the intervention. On the contrary, group 2 (control) consisted of 110 patients, aged 20–55 years (mean age 38.33 ± 8.72 years), who were treated without the use of a contrast agent.

Contrasting enabled to assess the size of the area that did not accumulate the contrast agent (theoretically, the zone of necrosis formed) and determine the completeness of the treatment of the pathological focus, the possibility of terminating the intervention, or the need to continue exposure.

Ultrasound ablation was performed under deep sedation (propofol + fentanyl). Tolerance to the procedure was assessed intraoperatively, according to the following parameters. The absence of painful sensations and motor activity of the patient was considered good; isolated cases of motor activity (slight displacement or change in the position of the abdomen) and sensations of moderate heating of the anterior abdominal wall, which required periodic cooling, were considered satisfactory; however, they did not affect the course of the surgery. The expressed motor activity of the patients and significant painful sensations during surgery, for which additional actions and pain relief were performed, indicated poor tolerance.

All quantifiable material was statistically processed using the Mann–Whitney test; the differences between the compared distributions of the populations were considered statistically significant at $p < 0.05$.

RESULTS

The average size of the dominant node, according to ultrasound scanning data, was 63.76 ± 24.34 cm^3 in group 1 and 45.34 ± 21.26 cm^3 in group 2.

About 70% of the nodes in both groups were located interstitially or interstitially and subserously. In half of the cases, the tumor was localized on the anterior or posterior wall of the uterus.

Intraoperative signs of changes in the structure of myomatous nodes exposed to HIFU included an increase in the echolucency of the node parenchyma and the emergence of hyperechoic areas. With the administration of an ultrasound contrast agent before, during, and after the procedure, the appearance of areas that did not accumulate the contrast was assessed. Sufficient efficiency was described as the appearance of an avascular zone with a size of at least 60% of the primary volume of the myomatous node.

Table 1. Parameters of high-intensity focused ultrasound ablation

Indicators	Follow-up groups		p
	study (n = 98)	control (n = 110)	
Duration of ablation, min	215.28 ± 70.57	610.84 ± 56.26	<0.005
Average energy, W	329.06 ± 33.06	293.68 ± 64.51	<0.001
Number of treated sections	5.59 ± 2.21	6.78 ± 2.61	<0.001

Table 2. Tolerability of high-intensity focused ultrasound ablation

Tolerability of ultrasound ablation	Follow-up groups		p
	study (n = 98)	control (n = 110)	
Unsatisfactory	1 (1.3%)	1 (0.9%)	>0.05
Satisfactory	6 (7.7%)	41 (37.3%)	<0.001
Good	71 (91%)	68 (61.8%)	<0.001

The duration of ultrasound ablation in group 1 was 215.28 ± 70.57 min (70–390 min), while in the control group, the duration of HIFU ablation was 610.84 ± 56.26 min (290–1230 min, $p < 0.005$), i.e., it was performed 2.8 times faster. No intra- or postoperative complications were noted in both groups (Table 1).

Contrasting produced a more accurate assessment of the results of the effect of HIFU on myomatous nodes, enabling the use of a significantly higher average energy in group 1 (329.06 ± 33.06 W) than in group 2 (293.68 ± 64.51 W) ($p < 0.001$), which in turn contributed to a reduction in the duration of the surgery.

The groups differed significantly in two indicators of HIFU tolerance: good and satisfactory; the patients from the study group tolerated the surgery significantly better (Table 2). Poor tolerance of ultrasound ablation in both groups did not differ significantly and was noted in one case from each group, which was 1.3% of patients in group 1 and 0.9% in group 2 ($p > 0.05$) (Table 2).

The duration of hospital stay in group 1 ranged from 3 to 9 days (on average 4.11 ± 2.36 bed-days) and from 2 to 14 days in group 2 (on average 4.53 ± 2.62 bed-days).

In group 1, an ultrasound of the small pelvis with dopplerometry, a month after ablation of the myomatous nodes by HIFU, revealed a decrease in their volume to 31.25 ± 14.87 cm³ (on average by 33.01 ± 17.72%) ($p < 0.005$). In group 2, the

volume of the nodes decreased to 42.92 ± 18.73 cm³, which amounted to 37.65 ± 17.36%. However, in four cases (3.6%) from the control group, the size of the treated nodes increased to 24%. Magnetic resonance imaging of the pelvic organs with contrast, one month later, showed that 96.7% of the patients in the study group and 73.2% of the patients in the control group developed a total zone of necrosis.

After six months, a significantly high ($p < 0.005$) regression of the mean node diameter was noted in both groups. In group 1, a decrease by 54.40 ± 22.07% was recorded (up to 23.48 ± 14.18 cm³ compared to the initial value of 45.34 ± 21.26 cm³). In group 2, the decrease in the size of nodes averaged 51.54 ± 35.03% (up to 35.01 ± 14.46 cm³ compared to the initial value of 63.76 ± 24.34 cm³).

The final visit of the patients, one year after treatment, revealed a significantly effective ($p < 0.005$) reduction in the size of the nodes, namely, in group 1, on average, by 62.5 ± 14.22% compared to their initial value (up to 17.95 ± 7.34 cm³) and in group 2, on average, by 61.61 ± 19.59% (up to 26.40 ± 10.23 cm³).

Therefore, based on our results, intraoperative contrast enhancement with SF₆ facilitates the use of submaximal and maximum ultrasound power for ablation of uterine fibroids with the use of HIFU, by reducing the time of insonation by 2.8 times and, in general, increasing the efficiency of treatment of uterine fibroids with modern noninvasive remote method.

REFERENCES

1. Karpov OE, Vetshev PS, Zhivotov VA. Ultrasound tumour ablation: the current status and new opportunities. *Bulletin of Pirogov National Medical Surgical Center*. 2008;3(2):77–82. [cited: 2021 Feb 14]. Available from: http://www.pirogov-vestnik.ru/upload/uf/3df/magazine_2008_2.pdf. (In Russ.)
2. Kira EF, Politova AK, Bolomatov NV, et al. Rezul'taty sochetannogo ispol'zovaniya selektivnoj jembolizacii i HIFU-abljacii u bol'nyh s miomoy matki. *Akusherstvo i ginekologija Sankt-Peterburga*. 2019;(3–4):18. (In Russ.)
3. Nazarenko GI, Chen VSh, Dzhan L, Hitrova AN. Ul'trazvukovaja abljacija-HIFU – vysokotehnologichnaja organosohranjajushhaja al'ternativa hirurgicheskogo lechenija opuholej. Moscow: MTs Banka Rossii; 2008. (In Russ.)
4. Slabozhankina EA. Vozmozhnosti ul'trazvukovoj abljacii (HIFU) v lechenii miomy matki. [dissertation abstract]. Moscow; 2014. [cited: 2021 Jan 23]. Available from: <https://www.dissercat.com/content/vozmozhnosti-ultrazvukovoi-ablyatsii-hifu-v-lechenii-miomy-matki>. (In Russ.)

5. Slabozhankina EA, Kitaev VM, Kira EF. The effectiveness of ultrasound hifu-ablation of uterine fibroids, depending on the type of mr fibroids // Bulletin of Pirogov National Medical Surgical Center. 2015;10(1):51–55. [cited: 2021 Feb 23]. Available from: http://www.pirogov-vestnik.ru/upload/uf/a52/magazine_2015_1.pdf. (In Russ.)
6. Lyon PC, Rai V, Price N, Shah A, Wu F, Cranston D. Ultrasound-guided high intensity focused ultrasound ablation for symptomatic uterine fibroids: Preliminary clinical experience. *Ultraschallgesteuerte hochintensive fokussierte ultraschallablation bei symptomatischen uterusmyomen: Eine vorläufige klinische erfahrung.* *Ultraschall Med.* 2020;41(5):550–556. DOI: 10.1055/a-0891-0729
7. Vilos GA, Allaire C, Laberge PY, Leyland N; SPECIAL CONTRIBUTORS. The management of uterine leiomyomas. *J Obstet Gynaecol Can.* 2015;37(2):157–178. DOI: 10.1016/S1701-2163(15)30338-8
8. Sonov'ju [Internet]. *Dinamicheskoe kontrastnoe usilenie v rezhime real'nogo vremeni.* Nauchnaja monografija. [cited: 2021 Jan 27]. Available from: <https://shopdon.ru/wa-data/public/site/blog/monografia-sonovyu.pdf>. (In Russ.)
9. Claudon M, Cosgrove D, Albrecht T, et al. Guidelines and good clinical practice recommendations for contrast enhanced ultrasound (CEUS) – update 2008. *Ultraschall Med.* 2008;29(1):28–44. DOI: 10.1055/s-2007-963785
10. Gramiak R, Shah PM. Echocardiography of the aortic root. *Invest Radiol.* 1968;3(5):356–366. DOI: 10.1097/00004424-196809000-00011
11. Greis C. Technology overview: SonoVue (Bracco, Milan). *Eur Radiol.* 2004;14 Suppl 8:P11–P15.
12. Lindner JR, Song J, Jayaweera AR, Sklenar J, Kaul S. Microvascular rheology of Definity microbubbles after intra-arterial and intravenous administration. *J Am Soc Echocardiogr.* 2002;15(5):396–403. DOI: 10.1067/mje.2002.117290

СПИСОК ЛИТЕРАТУРЫ

1. Карпов О.Э., Ветшев П.С., Животов В.А. Ультразвуковая абляция опухолей — состояние и перспективы // Вестник Национального медико-хирургического центра им. Н.И. Пирогова. 2008. Т. 3. № 2. С. 77–82. [дата обращения: 14.02.2021]. Доступно по ссылке: http://www.pirogov-vestnik.ru/upload/uf/3df/magazine_2008_2.pdf
2. Кира Е.Ф., Политова А.К., Боломатов Н.В. и др. Результаты сочетанного использования селективной эмболизации и HIFU-абляции у больных с миомой матки // Акушерство и гинекология Санкт-Петербурга. 2019. № 3–4. С. 18.
3. Назаренко Г.И., Чен В.Ш., Джан Л., Хитрова А.Н. Ультразвуковая абляция-HIFU – высокотехнологичная органосохраняющая альтернатива хирургического лечения опухолей. Москва: МЦ Банка России, 2008.
4. Слабожанкина Е.А. Возможности ультразвуковой абляции (HIFU) в лечении миомы матки: автореф. дис. ... канд. мед. наук. Москва, 2014. [дата обращения: 23.01.2021]. Доступно по: <https://www.disscat.com/content/vozmozhnosti-ultrazvukovoi-ablyatsii-hifu-v-lechenii-miomy-matki>
5. Слабожанкина Е.А., Китаев В.М., Кира Е.Ф. Эффективность ультразвуковой HIFU-абляции миомы матки в зависимости от МР-типов миоматозных узлов // Вестник Национального медико-хирургического Центра им. Н.И. Пирогова. 2015. Т. 10. № 1. С. 51–55. [дата обращения: 23.02.2021]. Доступ по ссылке: http://www.pirogov-vestnik.ru/upload/uf/a52/magazine_2015_1.pdf
6. Lyon P.C., Rai V., Price N., Shah A., Wu F., Cranston D. Ultrasound-guided high intensity focused ultrasound ablation for symptomatic uterine fibroids: Preliminary clinical experience. *Ultraschallgesteuerte hochintensive fokussierte ultraschallablation bei symptomatischen uterusmyomen: Eine vorläufige klinische erfahrung // Ultraschall. Med.* 2020. Vol. 41. No. 5. P. 550–556. DOI: 10.1055/a-0891-0729
7. Vilos G.A., Allaire C., Laberge P.Y., Leyland N.; SPECIAL CONTRIBUTORS. The management of uterine leiomyomas // *J. Obstet. Gynaecol. Can.* 2015. Vol. 37. No. 2. P. 157–178. DOI: 10.1016/S1701-2163(15)30338-8
8. Соновью [Internet]. *Динамическое контрастное усиление в режиме реального времени.* Научная монография. [дата обращения: 27.01.2021]. Доступно по: <https://shopdon.ru/wa-data/public/site/blog/monografia-sonovyu.pdf>
9. Claudon M., Cosgrove D., Albrecht T. et al. Guidelines and good clinical practice recommendations for contrast enhanced ultrasound (CEUS) — update 2008 // *Ultraschall. Med.* 2008. Vol. 29. No. 1. P. 28–44. DOI: 10.1055/s-2007-963785
10. Gramiak R., Shah P.M. Echocardiography of the aortic root // *Invest. Radiol.* 1968. Vol. 3. No. 5. P. 356–366. DOI: 10.1097/00004424-196809000-00011
11. Greis C. Technology overview: SonoVue (Bracco, Milan) // *Eur. Radiol.* 2004. Vol. 14. Suppl. 8. P. 11–15.
12. Lindner J.R., Song J., Jayaweera A.R., Sklenar J., Kaul S. Microvascular rheology of Definity microbubbles after intra-arterial and intravenous administration // *J. Am. Soc. Echocardiogr.* 2002. Vol. 15. No. 5. P. 396–403. DOI: 10.1067/mje.2002.117290

AUTHORS INFO

***Ekaterina A. Slabozhankina**, MD, PhD;
address: 70 Nizhnyaya Pervomayskaya str., Moscow, 105203, Russia;
e-mail: elfkat@mail.ru

Evgeniy F. Kira, MD, PhD, DSci (Medicine), Professor,
Honored Doctor of the Russian Federation, Honored Scientist
of the Russian Federation; e-mail: profkira33@gmail.com

Alla K. Politova, MD, PhD, DSci (Medicine);
e-mail: al1870@mail.ru

ОБ АВТОРАХ

***Екатерина Александровна Слабожанкина**, канд. мед. наук;
адрес: Россия, 105203, Москва, ул. Нижняя Первомайская, д. 70;
e-mail: elfkat@mail.ru

Евгений Федорович Кира, д-р мед. наук, профессор,
засл. врач РФ, засл. деят. науки РФ;
e-mail: profkira33@gmail.com

Алла Константиновна Политова, д-р мед. наук;
e-mail: al1870@mail.ru

AUTHORS INFO

Vyacheslav M. Kitayev, MD, PhD, DSci (Medicine),
Professor, Honored Doctor of the Russian Federation;
e-mail: vm_kitayev@list.ru

Sergey V. Bruslik, MD, PhD;
e-mail: drbruslik@mail.ru

Yulia L. Amelina, MD, Post-Graduate Student;
e-mail: doctoramelina@mail.ru

Alexandra A. Politova, Student;
e-mail: alexandra.politowa@mail.ru

ОБ АВТОРАХ

Вячеслав Михайлович Китаев, д-р мед. наук,
профессор, засл. врач РФ;
e-mail: vm_kitayev@list.ru

Сергей Владимирович Бруслик, канд. мед. наук;
e-mail: drbruslik@mail.ru

Юлия Леонидовна Амелина, аспирант;
e-mail: doctoramelina@mail.ru

Александра Александровна Политова, студент;
e-mail: alexandra.politowa@mail.ru