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Letrozole plus misoprostol versus misoprostol alone in the induction of anembryonic missed abortion: a randomized controlled trial conducted in Upper Egypt

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Abstract

Background A missed abortion is a spontaneous abortion in which the embryo or fetus has already died but has remained in the uterus for days or weeks with a closed cervical ostium. Termination of pregnancy could be achieved either by surgical evacuation or medical or expectant management. Letrozole is a third-generation aromatase inhibitor. According to many recent studies, letrozole given for three days before the administration of misoprostol was more effective than misoprostol alone at inducing abortion. Our study compared the efficacy of various letrozole regimens (10 mg/d for three days and a single dose of 20 mg) combined with misoprostol vs. misoprostol alone in inducing abortion. To find the most efficient regimen of letrozole administered before misoprostol to induce an abortion.

Methodology This prospective, parallel, three-arm, single-blinded, allocation-concealed randomized controlled trial was conducted in Sohag Teaching Hospital in Upper Egypt. We randomly divided 105 patients with anembryonic missed abortion (up to 63 days gestation) with no history of medical disorders or a history of allergies to misoprostol or letrozole into three equal groups (a single-dose letrozole group, a multiple-dose letrozole group, and a misoprostol-only group). The complete abortion rate, incomplete abortion rate, failure to abort rate, and induction-to-abortion interval were all collected. All statistical calculations were performed using the computer program SPSS (Statistical Package for the Social Science, SPSS Inc., Chicago, IL, USA).

Results The complete abortion rate was significantly higher in the single-dose letrozole and multiple-dose letrozole groups than in the misoprostol group (p values = 0.0455 and 0.001, respectively). On the other hand, there was no significant difference in the complete abortion rate between the single-dose group and the multiple-dose letrozole group (p-value = 0.1713). The time to complete abortion was significantly shorter in the single-dose and multiple-dose letrozole groups than in the misoprostol group (p values = 0.0036 and 0.0049, respectively). On the other hand, there was no significant difference in the time to complete abortion between the single-dose letrozole group and the multiple-dose letrozole group (P = 0.532).

Conclusion Single- and multiple-dose letrozole regimens followed by misoprostol had a higher rate and a shorter time to complete abortion than misoprostol alone.

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Trial registration The trial is registered at gov with the name "letrozole and abortion" and the identifier "NCT05198050". The date of registration was April 1, 2022, registered prospectively. URL: https://register.clinicaltrials.gov/prs/app/action/ViewOrUnrelease?uid=U0004GED&ts=25&sid=S000BPDQ&cx=43mobl.

Keywords Induction of missed abortion, Letrozole, Misoprostol

Background

A missed abortion is a spontaneous abortion in which the embryo or fetus has already died but has remained in the uterus for days or weeks with a closed cervical ostium [1]. Patients might present with or without subtle clinical symptoms such as vaginal bleeding or abdominal pain. Ultrasonography confirms missed abortions in 8–20% of clinically diagnosed intrauterine pregnancies [2].

Surgical evacuation is the standard treatment for missed abortions. Surgery has been widely performed in the past 50 years with a 95% success rate [3]. However, the surgery costs, the complications associated with it, hospitalization, and anesthesia remain significant unresolved concerns. Some studies have suggested that expectant or medical management might be more suitable than surgical evacuation [4, 5].

Active medical treatment of missed abortions induces a complete abortion faster than expectant management [6–8], and the reported success rates of medical treatment for missed abortions vary widely between 13 and 90% [9]. A dose of 800 mcg of vaginal or 600 mcg of sublingual misoprostol may be made available as an effective, safe, and acceptable alternative to surgical treatment for this indication**,** and the range of reported success rates in several studies is quite different (between 37 and 86%) [10]. Some studies suggest that prescribing aromatase inhibitors before misoprostol to induce medical abortion increases the efficiency of the treatment and decreases the need for surgical intervention [11–15]. Letrozole is a third-generation, nonsteroidal aromatase inhibitor licensed for breast cancer therapy that works by binding to the aromatase enzyme that catalyzes the rate-limiting step in the synthesis of estrogen, which converts androstenedione into estrone and testosterone into estradiol [16]. Estradiol plays a role in the maintenance of pregnancy in humans, and there are two possible mechanisms of action for letrozole in the termination of pregnancy. Letrozole may act directly on the corpus luteum in early pregnancy or placenta in later gestation, and the suppressed E2 synthesis could be detrimental to their functions, which may cause abortion or exert a synergistic effect on the induction of abortion with misoprostol [17].

Some studies have mentioned the enhancing effect of letrozole with misoprostol, but finding the optimal dose still requires more research [11–15]. Letrozole (10 mg/d for three days before misoprostol administration) seems more effective than misoprostol alone in inducing complete abortion [15]. A 20-mg single-dose regimen of letrozole for abortion induction is more effective, convenient, and potent. The dose of 20 mg was suitable based on calculations from previous pharmacodynamic investigations of letrozole, which showed 100% oral absorption and a half-time drug disappearance of 45 h [18]. Administering an aromatase inhibitor as a single dose provides the benefit of higher concentrations to achieve more potent aromatase inhibition; in addition, it is more convenient and may improve patient compliance by avoiding the need to remember to take three daily doses. Therefore, our study aim was to compare the effectiveness of various regimens of letrozole (10 mg/d for three days or a single dose of 20 mg) combined with misoprostol versus misoprostol alone in inducing complete abortion in patients with anembryonic missed abortion to find the most efficient regimen of letrozole administered before misoprostol to induce an abortion, and to determine whether it could help minimize the use of surgical evacuation for cases of miscarriage with its disadvantages. To the best of our knowledge, there are no randomized controlled trials that have investigated the efficacy of a single dose of letrozole (20 mg/d) before misoprostol in inducing complete abortion in patients with anembryonic missed abortion compared to a conventional regimen of letrozole (10 mg/d for three days before misoprostol) and a misoprostol-only regimen.

Methodology

Sample size calculation

A recent, randomized controlled trial revealed that letrozole (10 mg/d for three days before misoprostol administration) was more effective than misoprostol alone in inducing complete abortion [13]. We randomly allocated 32 patients to each arm of the trial with a study power of 80% at a significance level of 0.05 (two-tailed), and we expected that the dropout would be 8%, so 35 patients were recruited for each arm of the study. The dropouts of patients were because some patients did not complete their follow-up and others did not agree to give the authors consent (Fig. 1).

This prospective, parallel three-arm single-blinded allocation-concealed randomized controlled trial was conducted in Sohag Teaching Hospital in Upper Egypt between April 2022 and September 2022 to compare

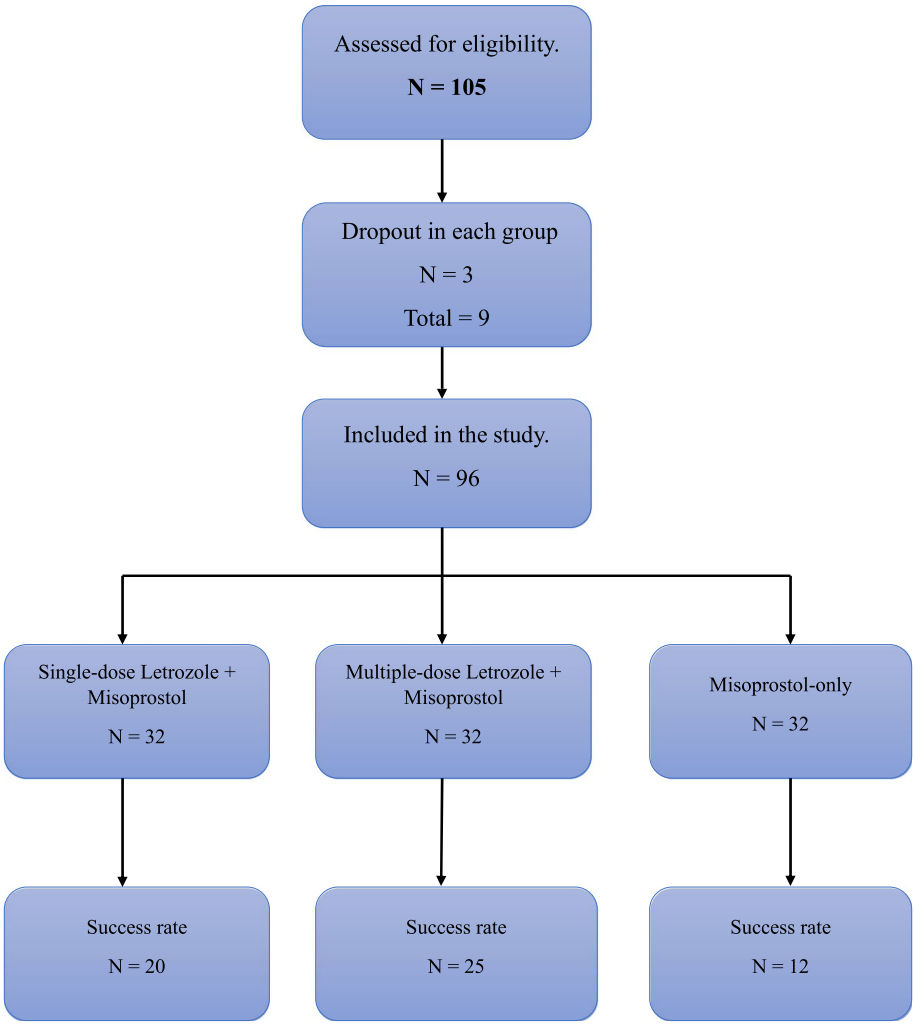

Fig. 1 Consort flow-chart of the cases outcome

the effectiveness of various regimens of letrozole (10 mg/d for three days and a single dose of 20 mg) combined with misoprostol vs. misoprostol alone in inducing an abortion to find the most efficient regimen of letrozole administered before misoprostol. We randomly divided 105 patients with anembryonic missed abortion (up to 63 days gestation) into three equal groups (a single-dose letrozole group, a multiple-dose letrozole group, and a misoprostol-only group) using a computer-generated randomization list and sequentially numbered sealed envelopes. The patients gave us informed consent before enrollment in the trial, and the institutional ethics committee approved the study protocol.

The inclusion criteria included maternal age (older than 18 years) and a first-trimester missed abortion (up to 63 days gestation) with an ultrasound picture of an anembryonic sac. The exclusion criteria included patients with medical disorders or a history of allergies to misoprostol or letrozole.

Patients in each group were given an 800-mcg dose of misoprostol, with one repeated dose after four hours if there was no response to the first dose. In the single-dose letrozole group, patients received a single dose of letrozole (20 mg) two days before starting misoprostol administration. Then, they were given placebo pills that resembled letrozole the day before and on the day of misoprostol treatment. In the multiple-dose letrozole group, patients received 10 mg of letrozole daily for two days before the misoprostol administration day and on the misoprostol administration day. In the misoprostol-only group, the patients received placebo tablets with a similar appearance to letrozole two days before and on the day of misoprostol administration.

Collected data included age, BMI, gestational age according to LMP, complete abortion rate, incomplete abortion rate, failure to abort rate, and induction-to-abortion interval. Patients who failed to abort, had severe bleeding, or had an incomplete abortion underwent dilatation and curettage operations. A transvaginal ultrasound was performed after 15 days to confirm a complete abortion.

The primary outcome was the complete abortion rate, and the secondary outcome was the induction-to-abortion interval (the interval between the administration of misoprostol and a complete abortion). To find the most efficient regimen of letrozole administered before misoprostol to induce an abortion.

Important definitions

Missed abortion: an in-utero death of the embryo or fetus before the 20th week of gestation with retained conception products in the uterus for days or weeks with a closed cervical ostium [1].

Complete abortion: is a complete passage of all conception products with an ultrasound picture of an empty uterus.

Incomplete abortion: is the partial loss of the products of conception. The ultrasound picture reveals the presence of some products of conception in the uterus.

The failure of abortion is the passage failure of conception products after drug induction.

Statistical analysis

Data were statistically described as the mean ± standard deviation (SD), median, range, frequencies (number of cases), and percentages when appropriate. We used Student's t test to compare the numerical variables and the chi-square ($\chi 2$) test to compare the categorical variables. *P* values of less than 0.05 were considered statistically significant. We performed all statistical calculations using the computer application SPSS (Statistical Package for the Social Sciences; SPSS Inc., Chicago, IL, USA).

Results

The three groups were comparable regarding age, BMI, and gestational age determined by LMP, as shown in Table 1.

Table 2 shows that the complete abortion rate was significantly higher in the single-dose letrozole group and multiple-dose letrozole group than in the misoprostol-only group (62.5% vs. 37.5%, p value = 0.0455; and 78.125% vs. 37.5%, p value = 0.001, respectively). On the other hand, there was no significant difference in the complete abortion rate between the single-dose group and the multiple-dose letrozole group (62.5% vs. 78.125%, p value = 0.1713).

There was no significant difference in the rate of incomplete abortion requiring surgical treatment in the single-dose letrozole group and multiple-dose letrozole group compared to the misoprostol-only group (9.37% vs. 21.875%, p value = 0.3017; and 6.25% vs. 21.875%, p value = 0.1504, respectively), or even between the

Table 1 Demographic criteria of the patients

	Group 1 Single dose letrozole ($n=32$)	Group 2 Multiple dose letrozole ($n=32$)	Group 3 Misoprostol ($n=32$)	G1 VS G2	G1 VS G3	G2 VS G3
Age	28.56 ± 6.34	29.81 ± 6.79	29.09 ± 6.13	0.45	0.73	0.66
BMI	24.62 ± 2.64	24.70 ± 2.41	24.45 ± 2.4	0.89	0.79	0.69
Gestational age	6.91 ± 0.29	7.09 ± 0.6	7.06 ± 0.25	0.14	0.09	0.78

Value are expressed as mean ± SD or n/n (%)

Table 2 Outcome of treatment

	Group 1 Single dose letrozole ($n=32$)	Group 2 Multiple dose letrozole ($n=32$)	Group 3 Misoprostol ($n=32$)	G1 VS G2 *p*-value	G1 VS G3 *p*-value	G2 VS G3 *p*-value
Complete abortion	20/32 (62.5%)	25/32 (78.125%)	12/32 (37.5%)	0.1713	0.0455	0.001
Incomplete abortion	3/32 (9.37%)	2/32 (6.25%)	7/32 (21.875%)	0.6414	0.3017	0.1504
Missed abortion	9/32 (28.12%)	5/32 (15.625%)	13/32 (40.625%)	0.2265	0.2925	0.0261
Time to complete abortion in hour	12.06 ± 3.75	12.76 ± 3.41	26.67 ± 13.73	0.532	0.0036	0.0049

Values are expressed as mean ± SD or n/n (%)

single-dose letrozole group and multiple-dose letrozole group (9.37% vs. 6.25%, p value = 0.6414). The failure to abort rate was significantly lower in the multiple-dose letrozole group than in the misoprostol-only group (15.625% vs. 40.625%, p-value = 0.026), while the failure to abort rate was comparable for the single-dose letrozole group and the misoprostol only group (Fig. 2). The time to complete abortion was significantly shorter in the single-dose letrozole and multiple-dose letrozole groups than in the misoprostol group (12.06 ± 3.75 h vs. 26.67 ± 13.73 h, p value = 0.0036, and 12.76 ± 3.41 h vs. 26.67 ± 13.73 h, p value = 0.0049, respectively). There was no significant difference in the time to complete abortion between the single-dose letrozole and the multiple-dose letrozole groups (12.06 ± 3.75 h vs. 12.76 ± 3.41 h, p value = 0.532) (Fig. 3).

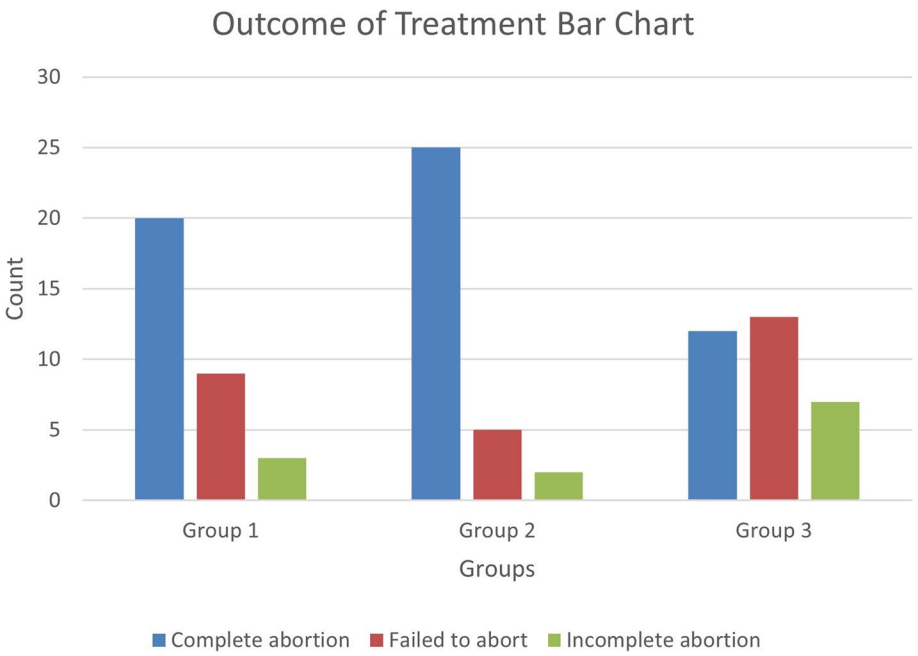

Fig. 2 Comparison of outcome of treatment between group

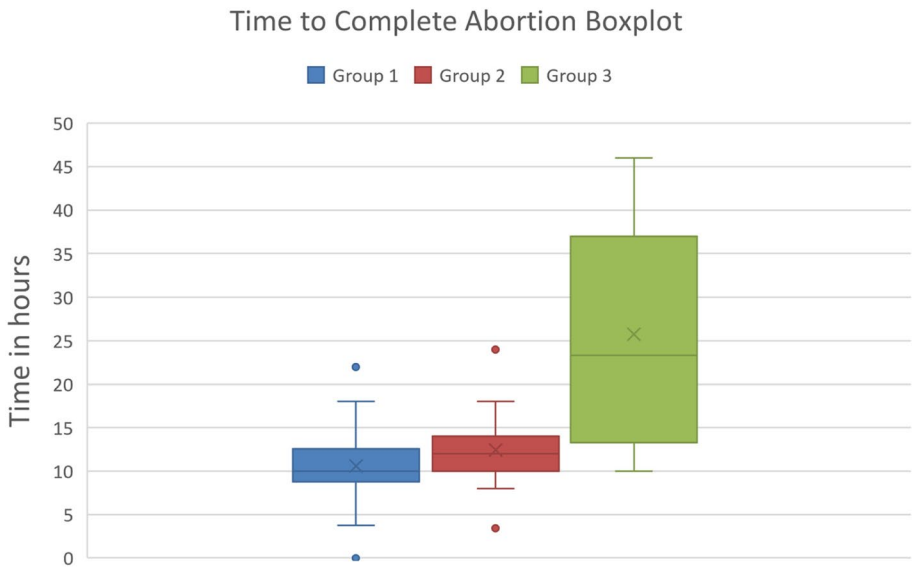

Fig. 3 Comparison of the time to complete abortion by hours between group

Discussion

Active medical treatment of missed abortions induces a complete abortion faster than expectant management [6–8]. Medical abortion decreases side effects such as bleeding, infection, and stress in patients compared with surgery. Numerous studies have reported using letrozole with misoprostol to induce abortion [19]. In the current study, the success rate of complete abortion was higher in the single-dose and multiple-dose letrozole regimens than in the misoprostol group (62.5% vs. 37.5%, $P=0.0455$; and 78.125% vs. 37.5%, $P=0.001$, respectively). There was no significant difference in the rate of incomplete abortion in the single-dose letrozole and the multiple-dose letrozole groups compared to the misoprostol-only group (9.37% vs. 21.875%, p value = 0.3017; and 6.25% vs. 21.875%, p value = 0.1504, respectively) or even between the single-dose letrozole and the multiple-dose letrozole groups. The failure to abort rate was significantly lower in the multiple-dose letrozole group than in the misoprostol-only group (15.625% vs. 40.625%, p-value = 0.026), while the failure to abort rate was comparable for the single-dose letrozole group and the misoprostol-only group. The time to complete abortion was significantly shorter in the single-dose letrozole group and multiple-dose letrozole group than in the misoprostol group (12.06 ± 3.75 h vs. 26.67 ± 13.73 h, p-value = 0.0036, and 12.76 ± 3.41 h vs. 26.67 ± 13.73 h, p value = 0.0049, respectively). There was no significant difference in the time to complete abortion between the single-dose letrozole and the multiple-dose letrozole groups (12.06 ± 3.75 h vs. 12.76 ± 3.41 h, p value = 0.532). Our results agree with the results of a randomized controlled trial in a series of 168 women of up to 63 days gestation that reported that the complete abortion rate was significantly higher in the letrozole group (10 mg/day for three days) followed by vaginal misoprostol 800 mcg than misoprostol alone (86.9% vs. 72.6%, $P=0.021$). The rate of incomplete abortions requiring surgical treatment was significantly lower in the letrozole group than in the misoprostol-alone group. The failure to abort rate was lower in the letrozole group, but the difference was statistically insignificant. The induction-to-abortion interval (8.2 h, range 3.3–711.6 h in the letrozole group, compared with 8.7 h, range 3.9–937.3 h in the misoprostol-alone group) was comparable for the letrozole and misoprostol-alone groups [17]. Our study results are comparable to those in other randomized controlled trials that compared the efficacy of letrozole (10 mg/day for three days) combined with misoprostol (800 mcg vaginally) vs. misoprostol alone. The complete abortion rate was significantly higher for the misoprostol and letrozole groups than for the misoprostol-alone group [14, 15, 20, 21]. A single-blinded clinical trial including 128 blighted ovum patients reported that the complete abortion rate was significantly higher in the letrozole (10 mg/day for three days) followed by misoprostol (600 mcg orally) regimen than in the misoprostol-only regimen (93.7% vs. 68.7%, $P=0.001$) [11], and these results agree with ours. A randomized controlled study in a series of 438 women revealed that the letrozole group (10 mg twice daily for three days) followed by misoprostol (800 mcg vaginally) had a significantly higher complete abortion rate (78% vs. 39%; $P<0.001$) and induction expulsion interval (mean in days is 1.33 ± 0.29 vs. 2.30 ± 0.64 and range in days is 1–3 vs. 1–4; $P<0.001$) [22]. These results agree with ours, but we used a different regimen for the multiple-dose letrozole group; patients received 10 mg of letrozole daily for two days before the misoprostol administration day and on the misoprostol administration day. As mentioned, most previous studies used multiple doses of letrozole before giving misoprostol. To the best of our knowledge, this was the first randomized controlled trial that compared the efficacy of a single dose of letrozole (20 mg/d) before misoprostol in inducing complete abortion in patients with anembryonic missed abortion to a conventional regimen of letrozole (10 mg/d for three days before misoprostol) and a misoprostol-only regimen.

A limitation of our study was the small sample size. Another limitation was the lack of measurement of serum E2 during the administration of letrozole, as this would determine the effect on the estrogen level. Another limitation of our study was the lack of measurements of serum calcium. If the woman took calcium supplements, this calcium would affect uterine contraction and act as a synergistic to misoprostol, which may affect our results. The cost of the multiple-dose regimen of letrozole (12 tablets) was high.

In conclusion, in cases of anembryonic missed abortion, single- and multiple-dose letrozole regimens followed by misoprostol had a higher rate of complete abortion in a shorter time than misoprostol alone. Therefore, both regimens are equally effective in inducing abortion. Administering a single-dose regimen of letrozole was more convenient and may improve patient compliance and determine whether it could help minimize surgical evacuation for cases of miscarriage. However, for its universal use, there is a need for more randomized controlled trials.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s43043-023-00152-8.

Additional file 1.

Additional file 2.

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Not applicable.

Authors' contributions
Conception and design of the study: SSZ and UF. Data collection: RH and MA. Data analysis and interpretation: UF. Statistical analysis: UF. Manuscript preparation: MA and RH. Recruitment of patients: RH. The authors read and approved the final manuscript.

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Availability of data and materials
The datasets used and analyzed during the current study are attached as a Supplementary file.

Declarations

Ethics approval and consent to participate
Ethical approval is attached as a Supplementary material document. The institutional review board approved the study protocol (code: MS-182–2021) in May 2021, and the authors obtained written informed consent from all patients before inclusion in the study.

Consent for publication
All patients provided written informed consent that the study results would be published.

Competing interests
The authors declare that they have no competing interests.

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