Global Medical and Health Communication

Online submission: https://ejournal.unisba.ac.id/index.php/gmhc
DOI: https://doi.org/10.29313/gmhc.v13i1.14144

GMHC. 2025;13(1):86–92
pISSN 2301-9123 | eISSN 2460-5441

RESEARCH ARTICLE

Effect of Umbilical Cord-derived Mesenchymal Stem Cell Secretome on Corpus Cavernosum Elastography Results in Patients with Severe Erectile Dysfunction Non-responsive to Sildenafil

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Abstract

Erectile dysfunction is one of the most common male sexual dysfunctions, defined as the inability to get or maintain an erection, and its prevalence is increasing over time. The current treatment, using a phosphodiesterase-5 inhibitor like sildenafil, only offers a temporary solution. Secretome, a bioactive substance derived from mesenchymal stem cells from the umbilical cord, has shown remarkable regenerative capabilities. This study aims to explore the potential of administering umbilical cord-derived mesenchymal stem cell secretome to patients with severe erectile dysfunction and evaluate its impact on the stiffness of the corpus cavernosum using elastography in the flaccid phase. This study employed a pre-experimental design with a pre-post test. It involved seven patients who came to Dr. Soetomo Hospital with severe erectile dysfunction that was unresponsive to sildenafil. Elastography evaluation, including strain and shear wave elastography, was performed before and one month after secretome injection, which was carried out from March to April 2024. Data were analyzed using the paired sample t-test when the data distribution was normal and the Wilcoxon test when the data distribution was not normal. There were statistically significant changes ($p<0.05$) in all patients who underwent strain and shear wave elastography of the corpus cavernosum before and one month after secretome administration, indicating an improvement in stiffness. In conclusion, intracavernosal administration of umbilical cord-derived mesenchymal stem cell secretome has demonstrated promising results in treating severe erectile dysfunction non-responsive to sildenafil therapy. These results include improved penile tissue in the corpus cavernosum, as evidenced by decreased stiffness on elastography.

Keywords: Elastography, erectile dysfunction, secretome

Introduction

Erectile dysfunction (ED) is defined as the inability to obtain or maintain an erection sufficient for satisfactory sexual intercourse. While no specific time is specified in this definition, some have suggested that the condition needs to persist for at least six months.[1] ED is a common condition that significantly affects men's quality of life. Globally, more than 150 million men suffer from ED. In the United States, the incidence rate is 25.9 cases per 1,000, and this rate increases with age. A study conducted by the Massachusetts Male Aging Study reported that the combined prevalence of mild and moderate ED in men aged 40–70 years was 52%. The causes of ED are often multifactorial; the etiology of ED is grouped into psychogenic, organic, or mixed, which usually involves both organic and psychogenic components.[2,3]

The severity of ED is determined by carefully evaluating various factors, including the onset of the condition, the relationship with the partner, erection rigidity, ejaculation without erection, and spontaneous erection at night. This evaluation can be done using a special questionnaire, such as the International Index of Erectile Function-5 (ED: total score: 25). The severity of ED can range from absence (22–25), mild (17–21), mild to moderate (12–16), moderate (8–11), to severe (1–7).[4]

Received: 26 September 2024; Revised: 28 April 2025; Accepted: 29 April 2025; Published: 30 April 2025

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In patients with ED, it leads to structural changes in the corpus cavernosum. These changes can be observed under an electron microscope as a decrease in the integrity of elastic tissue and an increase in collagen deposition between the cavernous sinusoids.[5] Elastography is an advanced technology that utilizes non-invasive ultrasound imaging to assess tissue stiffness, particularly in the corpus cavernosum. There are two main types of elastography: strain elastography and shear wave elastography (SWE). Strain elastography is a semi-quantitative method that relies on operator pressure, so the accuracy of the results depends on the user's skill. In contrast, SWE is a fully quantitative method that uses ultrasound waves to measure tissue stiffness in kilopascals (kPa) without applying pressure.[6]

Initially, treatment for ED involved administering androgens as an alternative form of psychotherapy. Currently, lifestyle adjustments are a crucial component of the therapeutic approach. The second approach, if known, involves addressing the underlying cause of the condition.[7] The primary treatment usually consists of oral phosphodiesterase-5 inhibitors (PDE5Is), which help to sustain an erection with appropriate sexual stimulation.[8] The secretome refers to the collection of molecules and biological factors that are secreted from cells into the extracellular space. These secretory factors play crucial roles in various biological functions, including homeostasis, development, signaling, immunomodulation, inflammation, angiogenesis, apoptosis, proteolysis, adhesion, and extracellular matrix organization.[9]

The first step in treating ED is often making lifestyle changes, such as losing weight, reducing alcohol intake, and avoiding smoking. Current therapies for treating ED primarily include oral PDE5Is, intracavernosal injections, hormone replacement therapy, vacuum erection devices, penile prostheses, low-intensity extracorporeal shock wave, and stem cell injection therapy.[8] The secretome comprises growth factors, cytokines, and other molecules with the potential to enhance tissue regeneration and improve erectile function; its application in Indonesian andrology is currently under development.[10] A previous study showed that umbilical cord mesenchymal stem cell therapy had a positive effect on degenerative structural changes in the corpus cavernosum tissue of diabetic animals. This study evaluated the effects using histology and concluded that MSC transplantation improved erectile performance according to the findings.[11] Based on these findings, mesenchymal stem cells from the umbilical cord could be a promising therapeutic approach for the treatment of ED. This study aimed to assess penile tissue stiffness and evaluate the effectiveness of administering secretome therapy to patients with severe ED in a non-invasive manner using elastography during the flaccid phase.

Methods

The study employed a pre-experimental design utilizing a pre-post-test approach, which was undertaken at the Department of Radiology of Dr. Soetomo General Academic Hospital from April to May 2024. Before the secretome injection, baseline measurements were obtained. Following the secretome injection, post-intervention assessments were conducted one month later. The disparity between the pre- and post-intervention observations signifies the efficacy of the intervention or therapy.

The inclusion criteria are patients aged 40–65 years who have had severe ED with organic factors for at least six months with an International Index of Erectile Function-5 (IIEF-5) score between 5–7, who already received sildenafil 100 mg 4 times, married and still living with his wife, type 2 diabetes mellitus with HbA1c examination results <7% and from the laboratory test the liver and kidney function tests are normal limits with a total of seven study subjects.

The exclusion criteria include patients with clinically visible anatomical abnormalities of the penis, those who have had systemic or local infections, a history of therapy for bleeding or blood clotting disorders, a history of systemic autoimmune disorders or immunosuppressive treatment, a history of prostate surgery, a history of malignancy or prostate-specific antigen (PSA) values >4 ng/ml, and untreated hypogonadism or low total serum testosterone (<200 µg/dl).

Examination using elastography in the flaccid phase is conducted to evaluate the stiffness of the corpus cavernosal tissue one month before and one month after intracavernosal injection of umbilical cord-derived mesenchymal stem cells (UC-MSC). Intracavernosal secretome injection using an ultra-thin needle with sterile protocol and guiding ultrasound. Intracavernosal secretome injection of 0.5 ml in the right and left corpus cavernosum was performed through the lateral aspect (3 and 9 o'clock directions). The

safety results of therapy were then assessed after injection, 24 hours, and 1 month. This evaluation encompasses the proximal, mid, and distal regions on both the right and left sides, utilizing strain elastography and shear wave elastography. Light pressure is applied to ensure that the transducer makes contact with the penis and that the patient should not experience any pain. This examination is conducted using a GE P8 USG machine with a linear probe.

The sampling technique used was consecutive, meaning that all subjects who met the inclusion criteria were included in the study until the required number of samples was reached. The patient then underwent anamnesis, completed the initial IIEF-5 and EHS questionnaires, and underwent a physical examination. Standard therapy was provided according to the Clinical Practice Guidelines. All subjects were subsequently sent to the radiology department for an ultrasound examination and consultation with a radiology specialist. The descriptive data presentation is conducted to analyze the characteristics of all the data and determine the mean and standard deviation values. The data were analyzed using SPSS 27.0 statistical software. In this study, we assessed the data for normality using the Shapiro-Wilk test on data from ultrasound reports before secretome injection and 1 month after secretome injection. If the data met the normal distribution, we employ the paired sample t-test for hypothesis testing. However, if the data distribution is abnormal, we use the Wilcoxon test. Our confidence level is 95%, and significance is determined by p-value<0.05. This study has been approved by the Health Research Ethics Committee of Dr. Soetomo General Hospital, as evidenced by the ethics permit number 0958/KEPK/IV/2024.

Results

Table 1 describes the characteristics of seven patients with severe ED who did not respond to sildenafil. Their average age was approximately 61 years. They showed normal liver and kidney function test results and had well-controlled type 2 diabetes mellitus. Additionally, the study included their PSA and testosterone levels, which were within normal limits, indicating that the patients were in good condition.

In Table 2, we conducted SWE measurements on the proximal, middle, and distal parts of the corpus cavernosum by placing a region of interest (ROI) with a minimum depth of 1 cm in various locations (Figure 1). The study found that before receiving secretome treatment, SWE value in the patient's corpus cavernosum ranged from an average of 9.25 to 10.31 kPa in the right corpus cavernosum and 10.56 to 11.09 kPa in the left corpus cavernosum.

Table 1 Characteristics of Research Subjects

Characteristics	n=50
Age, mean±SD	61.14±3.89
IIEF-5, median (min–max)	5 (5–7)
SGOT, mean±SD	21.57±6.70
SGPT, median (min–max)	16 (9–49)
Ureum, mean±SD	15.50±4.72
Creatinin, mean±SD	1.07±0.01
HbA1c, mean±SD	6.02±0.73
PSA, median (min–max)	1.40 (0.90–4)
Testosterone, mean±SD	675.6±302.27

After the patient was injected with secretome, ultrasound evaluations were conducted over one month. The average SWE value of the corpus cavernosum decreased to an average of 8.66 to 8.53 kPa on the right side and 8.96 to 9.64 kPa on the left side. The SWE values before and after secretome administration were analyzed using the Shapiro-Wilk normality test. The results showed a normal data distribution (p>0.05) on the right side and an abnormal distribution (p<0.05) on the left mid-distal SWE data. The right and left proximal SWE data were subjected to the Wilcoxon test when the data distribution was not normal and the paired t-test when the data distribution was normal. The results revealed a statistically significant decrease in SWE values in both the right and left corpus cavernosum, with p-values of 0.018 and 0.022, respectively (p<0.05).

According to the research analysis data provided in Table 3, the measurement of the strain ratio (SR) on the proximal side of the corpus cavernosum was conducted by comparing the stiffness between the surrounding normal tissue (refer to Figure 2), specifically the bulbospongiosus muscle and the corpus cavernosum tissue. The study results indicated that the SR of the patient's corpus cavernosum before receiving the secretome treatment was 1.53±0.46 in the right corpus cavernosum and 1.69±0.39 in the left corpus cavernosum. After the patient received the secretome treatment

Table 2 Results of SWE before and after Secretome Injection

Ultrasound Parameter	Pre-injection		Post-injection		p
	Mean±SD kPa	Median (Min–Max) kPa	Mean±SD kPa	Median (Min–Max) kPa	
SWE right proximal	9.25±1.55	9.01 (7.30–11.50)	8.66±1.44	8.90 (6.86–10.60)	0.018
SWE right mid	9.84±2.10	8.91 (7.80–13.20)	8.78±2.21	7.67 (6.57–12.40)	0.009
SWE right distal	10.31±3.61	9.50 (6.30–15.50)	8.53±2.08	9.27 (5.70–11.20)	0.034
SWE left proximal	10.56±2.22	10.50 (8.30–14.10)	8.96±1.50	8.26 (7.57–11.70)	0.018
SWE left mid	10.72±1.63	11.01 (8.89–13.07)	9.24±1.08	8.99 (8.11–11.01)	0.020
SWE left distal	11.09±2.80	12.80 (6.20–13.60)	9.64±2.05	9.40 (6.10–12.20)	0.039

and was evaluated one month later, the SR value decreased to 1.13±0.28 in the right corpus cavernosum and 1.30±0.30 in the left corpus cavernosum. The difference in SR was analyzed using the Shapiro-Wilk normality test, which revealed normal data distribution ($p>0.05$) in the left SR and abnormal data distribution ($p<0.05$) in the right SR. Subsequently, a paired t-test was conducted on the left SR, and a Wilcoxon test was conducted on the right SR. The results indicated a semi-quantitative decrease in stiffness values in both the right and left SR corpus, with p-values of 0.018 and 0.022, respectively, showing significant differences ($p<0.05$).

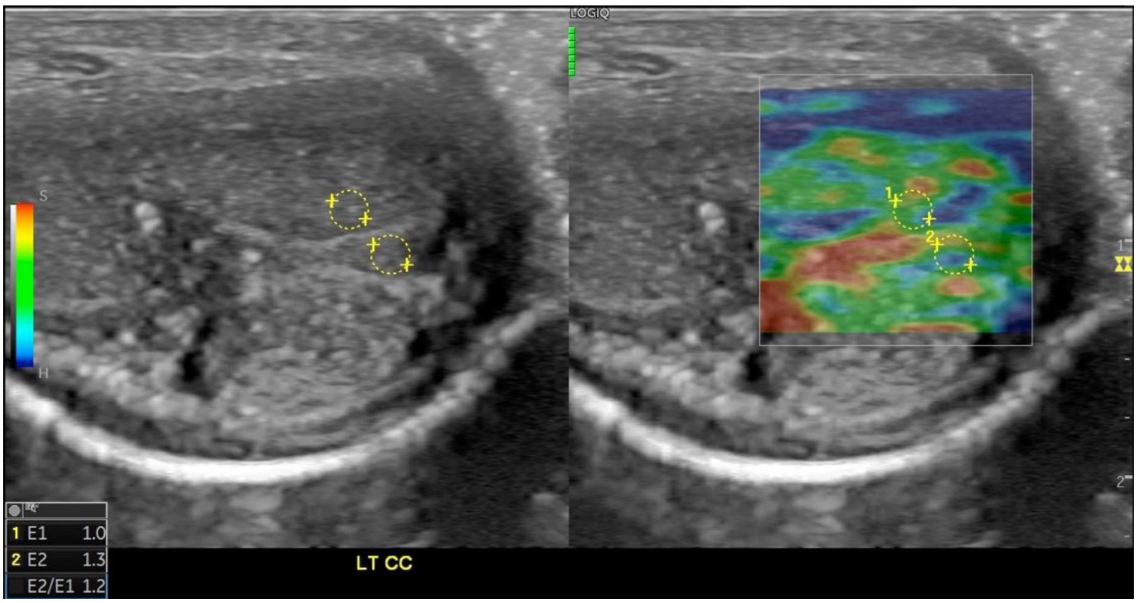

Figure 1 SWE Measurement from Corpus Cavernosum in the Region of Interest Example (Yellow Dot Line)
Note: color map elasticity in the square region with blue base color; a brighter color means the stiffer tissue

Table 3 Results of Strain Ratio before and after Secretome Injection

Ultrasound Parameter	Pre-injection		Post-injection		p
	Mean±SD kPa	Median (Min–Max) kPa	Mean±SD kPa	Median (Min–Max) kPa	
Right strain ratio	1.53±0.46	1.50 (1.00–2.30)	1.13±0.28	1.10 (0.80–1.70)	0.018
Left strain ratio	1.69±0.39	1.60 (1.20-2.30)	1.30±0.30	1.20 (1.00–1.80)	0.022

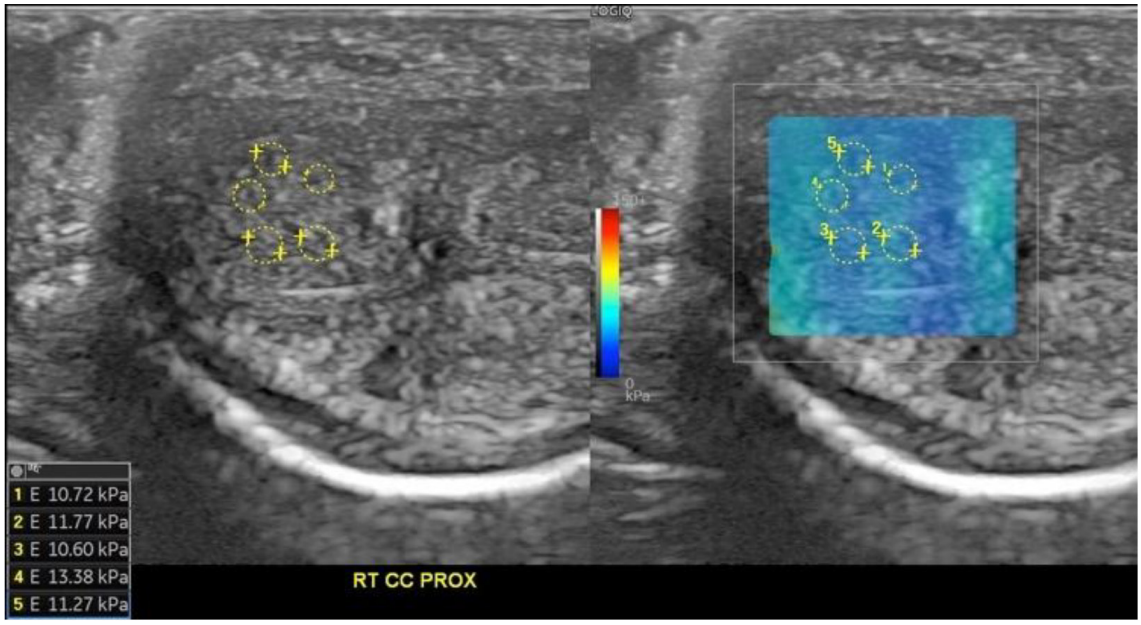

Figure 2 Strain Ratio Measurement Image on Corpus Cavernosum in the Region of Interest Example (Yellow Dot Line)
Note: color map elasticity in the square region was displayed in red (soft), green (intermediate), and blue (hard)

Discussion

Studies have shown that with increasing age, the incidence of ED increases. The link between aging and ED is partly based on the increasing rates of comorbidities experienced by older men, such as hypertension, vascular disease, chronic kidney disease, depression, and more. Diabetes is a risk factor for sexual dysfunction in men, with a three-fold increased risk of ED seen in men with diabetes compared to nondiabetic men.[12] The average values of urea, creatinine, SGOT, and SGPT are within normal limits, indicating that the kidneys and liver function well to excrete drug metabolites, thereby strengthening the safety of therapy and ensuring that drugs can be eliminated efficiently by the body, preventing the accumulation of potentially toxic substances.

The results of the elastography strain examination on the right and left sides showed a significant improvement. This improvement is attributed to the paracrine and regeneration factors present in the secretome. When stem cells are injected into the extracellular space, they can adapt to the needs of the affected anatomical structure and modify paracrine functions in specific tissues. According to previous research, animal experiments have demonstrated that intracavernosal injection of autologous and allogeneic mesenchymal stem cells can enhance erectile function in rats with cavernous nerve injury by increasing the average maximum intracavernosal pressure. The study suggests that the improved erectile function may be linked to the secretion of bioactive factors by the injected MSCs, which in turn reduces apoptosis, fibrosis, and inflammation in the corpus cavernosum.[13] The average elastography strain value before the procedure was 1.50 (1.00–2.30) on the right side and 1.69±0.39 on the left side, then decreased one-month evaluation after injection to 1.10 (0.80–1.70) on the right side and 1.30±0.30 on the left side with p-value <0.05. Previous studies with a larger sample size of ED patients obtained strain elastography values of <1.15. The author compared the arterial failure group and venous failure group, and the results showed the arterial failure group had a stiffer score of strain elastography.[14]

In this study, the statistical test yielded a p-value of less than 0.05 for the SWE results. The analysis results demonstrated significant improvement in the shear wave elastography results of severe ED patients who received secretome treatment. This improvement was reflected in the decreased stiffness of the corpus cavernosum on both the right and left sides after 30 days of secretome injection, as indicated by

the decrease in the kPa value on SWE. SWE is positively correlated with the material content, indicating stiffness in the presence of elastic, linear, or isotropic materials. A smaller SWE value indicates a better patient erection, while a higher SWE value indicates stiffer tissue.[15]

The corpus cavernosum is composed of smooth muscle cells (SMCs) and collagen, with SMCs playing a crucial role in its function. As a person ages, the onset of disease leads to a reduction in SMCs, as well as a decrease in elastic and collagen tissue. This can result in the blockage of the cavernous sinusoids, eventually leading to fibrosis and preventing the smooth muscles from relaxing. As a result, the cavernous sinusoids are unable to fill with blood appropriately.[16] Changes in the structure of the corpus cavernosum tissue directly result in changes in stiffness that can be observed in elastography. The more smooth muscle there is, the more elastic the tissue will be and the less stiff it will be. SWE utilizes an ultrafast imaging system to accurately capture tissue motion caused by shear wave propagation and monitor the speed of tissue motion in real time as the shear wave propagates through the scanning plane.[17,18] Another study demonstrated that a reduction in the number of SMCs led to higher measurements of SWE.

The study found that secretome administration led to improvements influenced by various factors in the secretome content, including regeneration and paracrine factors. Specifically, cells in the corpus cavernosum regenerated to become more elastic, and there was an increase in the number of SMCs. This led to an improvement in elastography, as indicated by a decrease in the strain ratio and kPa in SWE. SWE is an effective method for analyzing tissue stiffness based on cell type and tissue level. Previous studies have shown that the secretome has biological functions, including angiogenesis, development, anti-fibrotic, immunomodulatory, anti-apoptotic, and anti-inflammatory properties. These properties enable the secretome to adapt to damaged anatomical structures and modify them specifically in particular tissues.[9]

Other research results on local secretome injection were also studied for wound healing applications in radiation-induced skin. Weekly injections of secretome derived from human fetal skin-derived stem cells and UC-MSC effectively helped the wound healing process and angiogenesis through the effects of growth factors and pro-inflammatory and anti-inflammatory cytokines. Additionally, the healed tissue exhibited faster wound closure, less granulation tissue, and increased neovascularization.[19] In a separate study, diabetic mice that received injections of conditioned media from bone marrow mesenchymal stem cells showed improved wound closure and enhanced skin healing in chronic diabetic wounds. This was achieved through the modulation of fibroblasts, angiogenesis, and inflammatory and immune responses.[20]

The corpus cavernosum injected with secretome becomes more elastic, and the amount of fibrotic tissue is reduced, resulting in lower stiffness. To date, no human study has explained how ED can alter the measurement value of SWE. This is because DE is a complex condition, and the tissue's response to treatment can vary depending on the underlying cause.

This study utilized a pre-post test design. Our patients were followed up for one month after receiving secretome and were reevaluated using elastography. Our study is the first to show the effectiveness of administering secretome to patients with severe ED. It successfully improved the stiffness of the corpus cavernosum, as assessed using a non-invasive method called elastography. A single injection of secretome was found to enhance the stiffness of the corpus cavernosum in patients with ED.

The limitations of this study are the lack of evaluation time after the intervention; the sample size is less diverse because there are still few patients with severe ED who want to seek treatment in Indonesia, not comparing with the gold standard examination, namely biopsy, small sample size, and pre-post test design without a control group as a comparison, this can be explained because our study is still in the first clinical phase which has many limitations so that it will be continued in the second clinical phase.

Conclusions

The treatment involving the use of secretome from umbilical cord mesenchymal stem cells has shown positive results in patients with severe ED who do not respond to sildenafil. This therapy has been found to have a positive impact on the tissue in the corpus cavernosum. An alternative non-invasive evaluation method involves using elastography to measure tissue elasticity, which is closely related to tissue stiffness.

Conflict of Interest

The author declares that there are no conflicts of interest.

Acknowledgment

We would like to express our gratitude to all the lecturers of Radiology and Andrology at the Faculty of Medicine, Universitas Airlangga.

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