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ERECTILE DYSFUNCTION TREATMENT WITH COMBINATION OF MESENCHYMAL STEM CELL DERIVED EXOSOMES AND FOCUSED LOW-INTENSIVE SHOCK WAVE THERAPY

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ЛІКУВАННЯ ЕРЕКТИЛЬНОЇ ДИСФУНКЦІЇ КОМБІНАЦІЄЮ ЕКЗОСОМ, ОТРИМАНИХ З МЕЗЕНХІМАЛЬНИХ СТОВБУРОВИХ КЛІТИН І НИЗЬКОІНТЕНСИВНОЮ УДАРНО-ХВИЛЬОВОЮ ТЕРАПІЄЮ

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Summary

Relevance. Erectile dysfunction brings basic problem of urology, andrology and sexology. Erectile dysfunction have significant impact on quality of life, sexual and reproductive health and psychological condition in men. Novel experimental and clinical studies a several methods of regenerative medicine showed simultaneous impact on main pathogenetic aims showing significant levels of clinical efficacy.

Aim – to develop and analyze clinical effects of mesenchymal stem cell-derived exosomes intracavernous injections and low-intensity extracorporeal shock-wave therapy combination in patients with severe erectile dysfunction on background of metabolic syndrome and atherosclerosis.

Materials and methods. A prospective clinical study was conducted on a contingent of 38 patients of "Men's Health Clinic" (Kyiv, Ukraine) suffering from severe organic erectile dysfunction (ICD-10:N52.9; International index of erectile function score lower than 7) on the background of metabolic syndrome (ICD-10: E88.81) and generalized atherosclerosis (ICD-10: I70.9).

Study results. Therapeutics model of combined application of mesenchymal stem cell-derived exosomes intracavernous injections and low-intensity extracorporeal shock-wave therapy showed significant positive impact of applied therapeutic model according to IIEF-5, EHS scores as well as due to pharmacodoppler-sonography data. Therapeutics model of application low-intensity extracorporeal shock-wave therapy also showed significant positive impact on same diagnostic categories.

Conclusion. Comparison of post-therapeutic data between MG and CG showed absence of significant differences in all categories besides mean PSV, but values of statistical mistake probability are very close to significance threshold for IIEF-5 severe and moderate categories as well as EHS grades 4 and 2, what highlights perspective of further comparison studies on larger population scales, longer observation periods or less severe forms of ED.

Key words: regenerative medicine, erectile dysfunction, metabolic syndrome, exosomes, low-intensity extracorporeal shock-wave therapy.

Relevance. Erectile dysfunction (ED) brings basic problem of urology, andrology and sexology. ED has significant impact on quality of life, sexual and reproductive health

and psychological condition in men. Having complex pathogenesis that involves various factors besides of psychological, such as generalized and local biochemical imbalance,

vascular and neural pathology, local connective tissue degeneration, ED could not be effectively treated with therapeutic approaches focused on solitary pathogenetic aims [1, 2].

Phosphodiesterase fifth type inhibitors (PDE-5), as an erectogenic agent, have become the most prescribed group of drugs for ED treatment. In spite of the unambiguous symptomatic orientation of the action mechanism of PDE-5 not only doesn't demonstrate absolute effectiveness, but also, due to the marketing image of the "universal remedy", reduce patient's interest in pathogenetic and etiopathic therapy. Also patients with severe organic ED are typically having poor response to PDE-5 inhibitors. This leads to the acute demand to consider new, primarily bio- and physiotherapeutic options for ED treatment [2].

Novel experimental and clinical studies a several methods of regenerative medicine showed simultaneous impact on main pathogenetic aims of ED, showing significant levels of clinical efficacy. Among them as highly perspective particularly in ED treatment had been presented low-intensity shock wave therapy (LISWT), low-intensity pulsed ultrasound (LIPUS), platelet rich plasma (PRP) therapy, mesenchymal stem cell derived exosomes (MSC-DE) and human placenta hydrolysate (HPH) local application [2-16, 19, 20].

Studies focused on analysis of LISWT biological effects had demonstrated promising results in penile tissue regeneration due to multipotent mesenchymal stem cells (MSCs) biomechanical activation; angiogenesis stimulation due to increase of vascular endothelial growth factor (VEGF) production; positive impact on local hemodynamic by expression of endothelial and neuronal NO synthases (eNOS and nNOS) upregulation [3, 4].

Experimental and clinical data behind LIPUS method revealed its potential in penile connective, endothelial and smooth muscle tissue regeneration due to MSCs biomechanical activation; local tissue proliferation stimulation due to Rho/ROCK/Src/ERK1 signaling pathway regulation; increase of fibroblast growth factors (FGF), neural growth-related

factors such as brain derived neurotrophic factor (BDNF) and VEGF production; biomechanical stimulation of endothelial stem cells migration through the vascular wall into local tissues; positively modulating local perfusion by increasing eNOS and nNOS expression. Showing also decrease of collagen and fiber changes with down-regulation of TGF- β 1/ Smad/CTGF signaling pathway [5, 6].

Large group of studies of PRP therapy prove this method to be highly effective in penile tissue regeneration due to MSCs biosignaling activation; restoration of vascular wall endothelial membrane by stimulating the endothelial progenitor cells and correction of endothelial dysfunction by optimization of eNOS and nNOS production [3, 7, 8].

Analysis of MSC-DE therapy showed its effects on penile tissue regeneration; stimulation of myogenesis and angiogenesis by donating specific MCS growth-factors, specific biosignaling factors (extracellular matrix metalloproteinase inducer (EMMPRIN), non-coding RNAs (RNA H19) and regulatory miRNAs (miR210, miR126, miR132, miR21; miR-191, miR-222, miR-21, let-7a; miR-222, miR-21, let-7f; miR-6087); MSC-DE promotes neural tissue regeneration through a NOX2-PI3K-p-Akt signaling pathway; positively modulate endothelial functioning by eNOS, nNOS and VEGFR1 and VEGFR2 expression upregulation and modulation of signaling; performs anti-fibrotic and anti-apoptotic action protecting penile tissues by inhibiting caspase-3 dependent apoptosis pathway what is highly beneficial due penile smooth muscular cells protection [9 – 14].

Clinical studies on HPH therapy approved its effects in local tissue regeneration and anti-fibrotic activity by donating various growth factors such as VGEF, FGF, epidermal growth factor (EGF), neural growth factor (NGF), colony-stimulating factors (CSFs) and hormones dehydroepiandrosterone (DHEA) which is beneficial in some aspects of ED [15, 16].

Main biological aims and physiological mechanisms of LESWT, MCS-DE, RPR and HPH are summarized in table 1.

Table 1

Biological aims and physiological mechanisms of LESWT, MCS-DE, RPR and HPH

Biological aim	LESWT	MCS-DE	PRP	HPH
Activation of MSCs	↑PCNA	↑miRNAs (miR-191, miR-222, miR-21, let-7a); ↑non-coding RNAs (RNA H19)	↑TGF-β1	↑CSFs;
Connective tissue proliferation	↑bFGF;	indirect	indirect	↑bFGF;
Endothelial proliferation	↑VEGF	↑miRNAs (miR210, miR126, miR132, miR21); ↑EMMPRIN; ↑non-coding RNAs (RNA H19)	↑VEGF; ↑PDGF;	↑VEGF
Endothelial functioning	↑VEGF; ↑eNOS; ↑nNOS;	↑RNA H19; ↑eNOS; ↑nNOS; ↑VEGFR1 and VEGFR2	↑VEGF; ↑eNOS; ↑nNOS	↑VEGF
Protection of vascular wall	↑PCNA	indirect	↑PDGF	indirect
Neurometabolic effect	↑nNOS;	[NOX2-PI3K-p-Akt] activation; ↑nNOS;	↑IGF-1; ↑nNOS;	↑NGF

Abovementioned methods presented by promising experimental and clinical data in solving dominant groups of ED pathogenetic factors, however the models of its combined application is not developed yet. Our previous studies were focused on development and evaluation of clinical efficacy of therapeutic models where PRP-therapy and LISWT or LI-PUS are combined. Its results showed promising clinical data in contingents of patients with moderate ED cases.

Among the pharmacological agents that showed promising effect in moderate ED treatment due to our previous studies, we should mention Ikariin (ICA), the flavonoid of Epimedium brevicornum Maxim, that have similar biological activity to PDE-5, accompanied by stimulation of nitric oxide (NO) production and affinity to androgen receptors, what fits the elder patients pathogenetic profile.

Current project will consist of line of clinical studies focused on development of specific therapeutic model of combined regenerative therapy methods for patients with severe organic ED, starting with study on MSC-DE and LISWT combined application effects.

Aim – to develop and analyze clinical effects of MSC-DE intracavernous injections and LISWT combination in patients with severe ED on background of metabolic syndrome and atherosclerosis.

Materials and methods. A prospective clinical study was conducted on a contingent of 38 patients of "Men's Health Clinic" (Kyiv, Ukraine) suffering from severe organic erectile dysfunction (ICD-10:N52.9; International index of erectile function score lower than 7) on the background of metabolic syndrome (ICD-10: E88.81) and generalized atherosclerosis (ICD-10: I70.9). Study introduces line of inclusion and exclusion criteria.

Inclusion criteria:

- biological male sex;
- age 45-60;
- diagnosed and proved organic ED (presence of diagnostic criteria due to ICD-10 classification);
- "International index of erectile function" score lower than 7;
- sonographic proofs of vascular arterial and corporal veno-occlusive erectile dysfunction;
- diagnosed and proved metabolic syndrome (presence of diagnostic criteria due to ICD-10 classification and presence of corresponded documented medical history);
- diagnosed and proved generalized atherosclerosis (presence of diagnostic criteria due to ICD-10 classification and presence of corresponded documented medical history).

- patient not satisfied with response on PDE-5 inhibitors (due to objectively poor response).

Exclusion criteria:

- non-organic ED;
- oncologic pathology;
- hypogonadism;
- hypo- and hyperthyroidism;
- acute inflammatory pathology of prostatic gland;
- condition after prostatectomy;
- autoimmune and system pathology;
- significant psychopathology.

Study relied on following methods:

- standard set of clinical examinations;
- laboratory testing for hormone levels (LH, testosterone total, testosterone free, prolactine, estradiol, TTH, T4 free);
- questioner "International Index of Erectile Function-5" (IIEF-5) [17];
- clinical scale "Erectile Hardness Score" (EHS) [18];
- ultrasonic cavernous bodies scanning;
- pharmacodoppler-sonography.

Study results. Due to the purpose of a study initial contingent was divided in to two symmetrical groups: main group (MG) included 19 patients who underwent 6 weeks of combined treatment with 6 sessions of intracavernous MSC-DE injections (5,0 ml; one session per week) and 12 sessions of LISWT (3000 strikes, frequency 3 Hz, total power up to 0,35 mJ/mm² on standard penile areas; twice a week, each first session 30 minutes before MSC-DE injections and second session as a separate treatment technique) accompanied by 50mg of ICA as erectogenic agent and 1,0g of L-arginine aspartate (L-AA) as background metabolic therapy; control group (CG) included 19 patients who underwent 6 weeks of ED treatment with 12 sessions of LISWT (3000 strikes, frequency 3 Hz, total power up to 0,35 mJ/mm² on standard penile areas; twice a week), 50 mg of ICA and 1,0g L-AA. Both groups were undergoing metabolic syndrome and dyslipidemia treatment with provided by general practitioner (GP) what includes standard dietary restrictions, physical rehabilitation, metabolic and hypolipidemic therapy.

Therapy secludes presented in table 1.

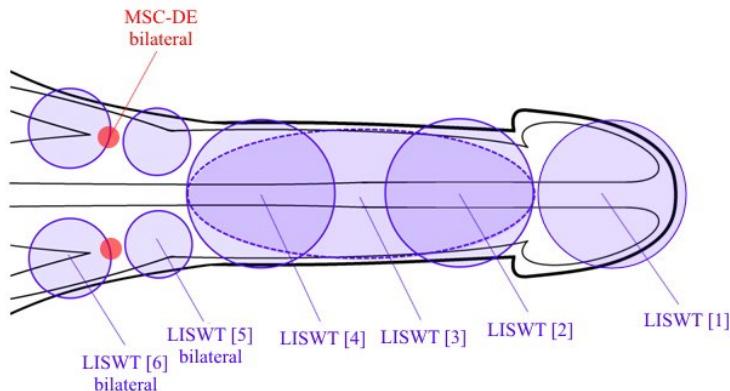
Table 2

Treatment models in MG and CG

Technique	Weeks					
	1-st	2-nd	3-rd	4-th	5-th	6-th
MG						
MSC-DE	5,0 ml	5,0 ml	5,0 ml	5,0 ml	5,0 ml	5,0 ml
LISWT	twice	twice	twice	twice	twice	twice
ICA	50 mg daily					
L-AA	1,0 g daily					
CG						
MSC-DE	none	none	none	none	none	none
LISWT	twice	twice	twice	twice	twice	twice
ICA	50 mg daily					
L-AA	1,0 g daily					

MSC-DE injections sessions were provided once a week 30 minutes after LISWT session by injecting 2,5 ml of solution intracavernously in each peduncles of penis. In 30 minutes LISWT session 3000 strikes, frequency 3 Hz,

total power up to 0,35 mJ/mm² on 6 standard penile areas to provide mechanical-induced trauma-simulating areas to focus MCS-DE regenerative potential. Combined session application presented on picture 1.



Pic. 1. Combined MSC-DE and LISWT sessions application.

In 12 weeks after the initial examination set IIEF-5, EHS and pharmacodoppler-sonography data was compared to pre-therapeutic in MG (table 3) and CG (table 4).

Table 3
Pre-therapeutic and post-therapeutic data comparison for MG

Criterion	Pre-therapeutic	p	Post-therapeutic
International Index of Erectile Function-5			
Mild (21-17 points)	0	-	0
Mild-moderate (16-12 points)	0	<0,01	6
Moderate (11-8 points)	0	<0,01	12
Severe (< 7 points)	19	<0,01	1
Erectile Hardness Score			
Grade 1	0	0,31	1
Grade 2	0	0,05	7
Grade 3	2	<0,01	9
Grade 4	17	<0,01	2
Pharmacodoppler-sonography			
Mean PSV in stimulation (cm/s)	23,4±0,3	<0,01	29,6±0,3
Mean EDV in stimulation (cm/s)	5,4±0,2	<0,01	4,5±0,3

Data comparison in MG shows significant positive impact of applied therapeutic model according to IIEF-5, EHS scores as well as due to pharmacodoppler-sonography data. However therapeutic effects are limited due to revealed post-therapeutic distribution of IIEF-5 (where 63,2% patients stayed on moderate

level of severity, 31,6% of patients achieved mild-moderate level and no one achieved mild level) and EHS (where 47,4% patients stayed on 3-nd grade, 36,8% of patients achieved 2-nd grade and only 1 (5,3%) patient achieved 1-st grade) scores.

Table 4

Pre-therapeutic and post-therapeutic data comparison for CG

Criterion	Pre-therapeutic	p	Post-therapeutic
International Index of Erectile Function-5			
Mild (21-17 points)	0	-	0
Mild-moderate (16-12 points)	0	<0,01	7
Moderate (11-8 points)	0	<0,01	7
Severe (< 7 points)	19	<0,01	5
Erectile Hardness Score			
Grade 1	0	-	0
Grade 2	0	0,07	3
Grade 3	2	0,03	9
Grade 4	17	<0,01	7
Pharmacodoppler-sonography			
Mean PSV in stimulation (cm/s)	23,4±0,3	<0,01	25,4±0,3
Mean EDV in stimulation (cm/s)	5,4±0,2	0,24	4,8±0,3

Data comparison in MG shows significant positive impact of applied therapeutic model according to IIEF-5, EHS scores. Pharmacodoppler-sonography data reveals significant positive effect only on mean PSV, but not for mean EDV. Post-therapeutic distribution of IIEF-5 scores (36,8% patients stayed on moderate level of severity, 36,8% of patients achieved

mild-moderate level and no one achieved mild level) and EHS (where 47,4% patients stayed on 3-nd grade, 15,8% of patients achieved 2-nd grade and no one achieved 1-st grade) reveals limitations of therapeutic model.

Differences between post-therapeutic status of MG and CG patients presented in table 5.

Table 5

Post-therapeutic data comparison between MG and CG

Criterion	MG	p	CG
International Index of Erectile Function-5			
Mild (21-17 points)	0	-	0
Mild-moderate (16-12 points)	6	0,73	7
Moderate (11-8 points)	12	0,10	7
Severe (< 7 points)	1	0,08	5
Erectile Hardness Score			
Grade 1	1	0,31	0
Grade 2	7	0,14	3
Grade 3	9	1,00	9
Grade 4	2	0,06	7
Pharmacodoppler-sonography			
Mean PSV in stimulation (cm/s)	29,6±0,3	<0,01	25,4±0,3
Mean EDV in stimulation (cm/s)	4,5±0,3	0,48	4,8±0,3

Comparison of post-therapeutic data between MG and CG showed absence of significant differences in all categories besides mean PSV, but values of statistical mistake probability are very close to significance threshold for IIEF-5 severe and moderate categories as well as EHS grades 4 and 2, what highlights perspective of further comparison studies on larger population scales, longer observation periods or less severe forms of ED.

Also remarkable the non-equal appearance in both groups of a study patients who have positive response on PDE-5 inhibitors: in MG – 15 (78,9%) patients, in CG – 10 (52,6%) patients, what is not significant ($p=0,08$), but also seems to be promising for further studies.

Conclusions. Developed ED therapeutic model which combine application of MSC-DE and LISWT on background of ICA and L-AA prescription showed significant positive impact on ED severity level due to IIEF-5 data, significant positive impact on erectile

hardness due to EHS data and significant positive impact on erectile haemodynamics due to pharmacodoppler-sonography data. It was found that therapeutic effects are limited due to revealed post-therapeutic distribution where 63,2% patients stayed on moderate level of severity, 31,6% of patients achieved mild-moderate level and no one achieved mild level according to IIEF-5 score, according to EHS score 47,4% patients stayed on 3-nd grade, 36,8% of patients achieved 2-nd grade and only 1 (5,3%) patient achieved 1-st grade. Nevertheless due to intentional complexity of ED genesis in study contingent results obtained should be considered as positive and perspective. Comparison of therapeutic models efficacy revealed lack significant differences in all categories besides mean PSV, but values of statistical mistake probability are very close to significance threshold for IIEF-5 severe and moderate categories as well as EHS grades 4 and 2.

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РЕЗЮМЕ

ЛЕЧЕНИЕ ЭРЕКТИЛЬНОЙ ДИСФУНКЦИИ КОМБИНАЦИЕЙ ЭКЗОСОМ, ПОЛУЧЕННЫХ ИЗ МЕЗЕНХИМАЛЬНЫХ СТВОЛОВЫХ КЛЕТОК И НИЗКОИНТЕНСИВНОЙ УДАРНО-ВОЛНОВОЙ ТЕРАПИЕЙ

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Актуальность. Эректильная дисфункция создаёт базовые проблемы урологии, андрологии и сексологии. Эректильная дисфункция оказывает значительное влияние на качество жизни, сексуальное и репродуктивное здоровье и психологическое состояние мужчин. Новые экспериментальные и клинические исследования методов регенеративной медицины обнаружили потенциал воздействия данных методов на основные патогенетические цели, демонстрируя значительный уровень клинической эффективности.

Цель – разработать и проанализировать клинические эффекты комбинации интракавернозных инъекций экзосом мезенхимальных стволовых клеток и низкоинтенсивной экстракорпоральной ударно-волновой терапии у пациентов с тяжелой эректильной дисфункцией на фоне метаболического синдрома и атеросклероза.

Материалы и методы. Проспективное клиническое исследование было проведено на контингенте из 38 пациентов «Клиники «Мужское здоровье»» (Киев, Украина), страдающих тяжелой органической эректильной дисфункцией (МКБ-10: N52.9; Международный индекс эректильной функции менее 7 баллов) на фоне метаболического синдрома (МКБ-10: E88.81) и генерализованного атеросклероза (МКБ-10: I70.9).

Результаты исследования. Терапевтическая модель комбинированного применения интракавернозных инъекций экзосом мезенхимальных стволовых клеток и низкоинтенсивной экстракорпоральной ударно-волновой терапии показала значительное положительное влияние в соответствии с оценками МИЭФ-5 и шкалы жесткости эрекции, а также данными фармакодопплерографии. Терапевтическая модель применения низкоинтенсивной экстракорпоральной ударно-волновой терапии (без включения экзосом) также показала значительное положительное влияние на указанные диагностические категории.

Вывод. Сравнение посттерапевтических данных в группах исследования показало отсутствие значимых различий во всех диагностических категориях, кроме среднего ПСС. При этом значения вероятности статистической ошибки очень близки к порогу значимости для категорий тяжелой и средней степени тяжести МИЭФ-5, а также для 4

и 2 степени шкалы жесткости эрекции, что подчеркивает перспективы исследований на больших популяциях, более длительных периодах наблюдения или менее тяжелых формах эректильной дисфункции.

Ключевые слова: регенеративная медицина, эректильная дисфункция, метаболический синдром, экзосомы, низкоинтенсивная экстракорпоральная ударно-волновая терапия.

РЕЗЮМЕ

ЛІКУВАННЯ ЕРЕКТИЛЬНОЇ ДИСФУНКЦІЇ КОМБІНАЦІЄЮ ЕКЗОСОМ, ОТРИМАНИХ З МЕЗЕНХІМАЛЬНИХ СТОВБУРОВИХ КЛІТИН І НИЗЬКОІНТЕНСИВНОЮ УДАРНО-ХВИЛЬОВОЮ ТЕРАПІЄЮ

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Актуальність. Еректильна дисфункция створює базові проблеми урології, андрології та сексології. Еректильна дисфункция значно впливає на якість життя, сексуальне і репродуктивне здоров'я та психогічний стан чоловіків. Нові експериментальні і клінічні дослідження методів регенеративної медицини виявили потенціал впливу даних методів на основні патогенетичні цілі, демонструючи значний рівень клінічної ефективності.

Мета – розробити і проаналізувати клінічні ефекти комбінації інтракавернозних ін'єкцій екзосом мезенхімальних стовбурових клітин і низькоінтенсивної екстракорпоральної ударно-хвильової терапії у пацієнтів з важкою еректильною дисфункциєю на фоні метаболічного синдрому і атеросклерозу.

Матеріали та методи. Проспективне клінічне дослідження було проведено на контингенті з 38 пацієнтів «Клініки «Чоловіче здоров'я»» (Київ, Україна), із тяжкою формою органічної еректильної дисфункциї (МКХ-10: N52.9; Міжнародний індекс еректильної функції менше 7 балів) на тлі метаболічного синдрому (МКХ-10: E88.81) і генералізованого атеросклерозу (МКХ-10: I70.9).

Результати дослідження. Терапевтична модель комбінованого застосування інтракавернозних ін'єкцій екзосом мезенхімальних стовбурових клітин і низько інтенсивної екстракорпоральної ударно-хвильової терапії показала значний позитивний вплив відповідно до оцінок МІЕФ-5 і шкали жорсткості ерекції, а також за даними фармакодопплерографії. Терапевтична модель застосування низькоінтенсивної екстракорпоральної ударно-хвильової терапії (без включення екзосом) також показала значний позитивний вплив на зазначені діагностичні категорії.

Висновок. Порівняння посттерапевтичних даних в групах дослідження показало відсутність значущих відмінностей у всіх діагностичних категоріях, крім середнього ПСШ. При цьому значення ймовірності статистичної помилки дуже близькі до порогу значущості для категорій тяжкого та середнього ступеня тяжкості МІЕФ-5, а також для 4 і 2 ступеня шкали жорсткості ерекції, що підкреслює перспективи досліджень на більших популяціях, більш тривалих періодах спостереження або менш важких формах еректильної дисфункциї.

Ключові слова: регенеративна медицина, еректильна дисфункция, метаболічний синдром, екзосома, низько інтенсивна екстракорпоральна ударно-хвильова терапія.

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