

Laparoscopic Intraovarian Injection of Cerebrolysin a New Modality for Treatment of Unexplained Infertility

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Abstract: To evaluate laparoscopic intraovarian injection of cerebrolysin in the treatment of unexplained infertility prospective study. Heliopolis Infertility Research Centre. 100 unexplained infertility patients divided into 2 equal groups I, II (group I study, group II control group). In group I 10 ml cerebrolysin laparoscopically injected in each ovary, in group II (no injection) control. Pregnancy rate after 4 months follow-up was determined after 4 months follow up period pregnancy rate in group I was 50% comparable to 4% in the control group. Statistically highly significant. Cerebrolysin is a new modality for treatment of unexplained infertility with no reported side effects after 4 months follow-up.

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1. Introduction:

It was estimated by the world health organization that one in six couples experience a delay in conception and conventional fertility tests fail to detect a cause in either partner in as many as 40% of such couples^[1].

The therapy for unexplained infertility is by empiric. The proposed treatment regimens include intrauterine insemination, superovulation with oral and injectable medication, combination of IUI with superovulation and the assisted reproductive technologies^[1, 2].

Based on our previous work^[3] that there was statistically decreased preovulatory follicular fluid Brain Derived Neurotrophic Factor (BDNF) in unexplained infertility than in control and that cerebrolysin increase production of BDNF, we conduct this work for direct injection of cerebrolysin in the ovary through laparoscopy in unexplained infertility^[3].

2. Material and Method:

Fifty patients complaining from unexplained infertility experienced failure of previous established line for treatment of unexplained infertility were enrolled in the study (group 1). The mean age was 38.2±3.2.years. The mean duration of infertility was 9.2±1.2.years Laparoscopy was done as usual; cerebrolysin was injected directly in each ovary, 10 ml in each ovary: 5 ml was given at 12 o'clock and 5 ml was given at 6 o'clock in each ovary.

Fifty patients with unexplained infertility were subjected to laparoscopy in the routine assessment for unexplained infertility with no injection (group 2), with mean age of 38.9 ± 2.5 years and the mean duration of infertility was 9.5 ± 1.3 were enrolled as a control group, follow up of the patients for pregnancy for 4 months.

Statistical analysis:

Pregnancy rate is expressed as a number of pregnancies after 4 months follow up. Statistical analysis of significance between both 2 groups was calculated by using t test, A *P* value of < 0.05 is considered statistically significant.

Ethics:

The study was performed in accordance with the guide lines in the Declaration of Helsinki and has been formally approved by the local ethical committee. Informed consent was obtained from all patients.

3. Results:

Results will be summarized in table 1 and 2. Table 1 shows that there was no statistical difference between the 2 groups regarding age, BMI and duration of infertility (*P*>0.05) but there was a statistical difference between the 2 groups regarding pregnancy rate after 4 months (*P*<0.01).

Table 2 shows that pregnancy rate is more in previous failed ART.

Table (1): represents the patients characteristics for group 1(cerebrolysin group) and group 2 (control group) and pregnancy rate after 4 months.

	Group 1	Group 2
Age	38.2±3.2	38.9±2.5
BMI	23.44±3.11	23.11±2.99
Duration of infertility	9.2±1.2	9.5±1.3
Pregnancy rate	25 (50%)	2 (4%)

Table (2): pregnancy rate after intraovarian injection of cerebrolysin in relation to previous failed methods of treatment of unexplained infertility in group 1

Method of treatment	No.	Pregnancy rate	
		No.	%
IUI	5/50	2	40
Superovulation	15/50	5	33.3
IUI and Superovulation	10/50	6	60
ART (GIFT, IVF, ICSI)	20/50	12	60

4. Discussion:

Therapy of unexplained infertility is empiric. Proposed treatment regimens include intrauterine insemination (IUI), superovulation with oral and injectable medications, combination of IUI with superovulation and the assisted reproductive technologies (ARTs) IVF, ICSI [1,2]. Based on our previous work that in unexplained infertility there was decreased level in follicular BDNF. We used intraovarian injection of cerebrolysin^{3,4}.

Cerebrolysin (Ebew pharma, Austria) it is unique effective and safe treatment of stroke, Dementia, brain injuries, Neuroprotective, neurotrophic, Alzheimer's, vascular dementia, very wide margin of safety, is unique because it contains biologically active peptides act as neurotrophic and neuroprotective factors in brain, it protects neurons from ischemia, hypoxia, toxic lesions counteracted the *in vitro* effect of glutamate, it has neurotrophic activity similar to nerve growth factor.

Cerebrolysin is a unique neurotrophic drug containing biologically active peptides⁵. cerebrolysin is a biotechnological preparation consisting of an aqueous solution of 15% peptides with a molecular weight not exceeding 10 KD and 85% amino acid based on the total nitrogen, the solution, ready for injection, infusion, is free of proteins, lipids and has no antigenic properties⁶. It has four functions: antioxidant⁷, neurotrophic stimulation⁸ cerebrolysin with its unique neurotrophic effect secures the survival, differentiation and protects neurons from toxic and noxious factors⁹, neuromodulation¹⁰ : it induces changes of neuronal and synaptic plasticities and metabolic regulation, cerebrolysin protects the nerve cells of the brain from a possible lactate acidosis and improves oxygen utilization inside the nerve cells. Cerebrolysin is available in 1 ml, 5 ml and 10 ml

ampoules and 20 ml, 30 ml and 50 ml vials, single doses up to 50 ml can be administered. As the increased dosages of cerebrolysin lead to increased neurotrophic effect we use the dose 100 ml in each ovary.

No severe side effects or adverse drug effects of cerebrolysin were reported in clinical trials¹¹, an extremely wide margin of safety is calculated for cerebrolysin. Hypersensitivity to one of the components of the drug, Epilepsy and severe renal impairment is the known contraindications of the drug, on the basis of cerebrolysin pharmacological profile, special attention should be given to a possible additive effects when used in conjunction with antidepressant or MAO inhibitors. Regarding overdosage there are no known instances of health related negative effects due to over dosage or intoxication¹².

Reviewing the literature regarding the pregnancy rate with previous already established line of treatment of unexplained infertility in IUI¹¹, CC^{1,2}, CC/IUI^{1,2}, HMG¹⁴, GIFT, IVF, ICSI^{15,16} was ranged from 4.76% to 40%

In this work we found a pregnancy rate (was diagnosed by serum β -HCG and 3D transvaginal ultrasound) after intraovarian injection of cerebrolysin was 50% after 4 months follow up compared to 4% in the control group which was statistically highly significant, Table 1 ($P < 0.01$).

Regarding the pregnancy rate in relation to previous failed methods of treatment of unexplained infertility in group 1 we found pregnancy rate is more with previous failed ART 60%.

There were no reported complications in the study group and the patients' compliance was satisfactory.

Conclusion:

Cerebrolysin is a new modality for cases of unexplained infertility with high pregnancy rate compared to controls. The drug is well tolerated and no side effects reported. However more randomization is needed before testing the efficacy of this new line of treatment.

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