Myth and Reality Application of Magnetite Nanoparticles as Selective Contrasting Means of the Malignant Tumors in MRI Investigation

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***Abstract*- In an experiment it is shown on rats, that biocompatible standardized nanoparticles of ICNB can be effectively used at MRI. It is well-proven that nanoparticles of ICNB for certain ($p<0.001$) strengthen a contrasting effect at MRI. Methodology of safe intravenous application of ICNB is excluding the use of magnetite of nanoparticles in the variant of independent contrasting means at MRI. It is set that in 24 hours after intravenous inject of ICNB the magnetite of nanoparticles for certain ($p<0.001$) selectively accumulate in tissue of malignant tumour and rise brightness of image. On 4th days investigation the dynamics of reduction of brightness of image in tumour and muscles was establishment for certain ($p<0.001$). This fact is caused by process eliminating of nanoparticles from organism of rat. On the mechanism of action the nanoparticles of ICNB cause the convertible changes which is reason for the temporal increase of mobility of protons of hydrogen in near cell liquid. It inevitably modifies the metabolic process in malignant cells that in perspective has hope in elaborating new ways of the target therapy of malignant neoplasm.**

Keywords- Nanoparticles; Magnetic; ICNB; MRI; Malignant Tumour; Contrast; Selectively

I. INTRODUCTION

Idea of using magnetite of nanoparticles as contrasting means in MRI investigation is not new. Objectively it follows from physical properties of nanoparticles. Scientific literature abounds in information about the use of magnetite of nanoparticles as contrasting means [1-5]. Separate actuality application magnetite of nanoparticles has early MRI diagnostics and target therapy of malignant tumors. In spite of the fact that application of magnetite of nanoparticles looks simple, it is not necessary to forget about a high danger of the origins of complications as a result of their intravessel inject. At least it is necessary to take into account such indexes as a concentration, doze, rate of entered solution of nanoparticles, time of allocation nanoparticles in blood circulation after inject. The enumerated parameters for reliable have influence on haemorreology and state of microcirculation on the whole. The high local concentration of magnetite in vessels is caused by disturbances of blood circulation, microcirculation and hypoxia of tissues [6, 8]. It is dangerous in main vital organs: brain, heart, lungs, liver and kidneys. Direct cross-correlation dependence between concentration of nanoparticles and level hypoxia is physiopathology obvious. Consequently, before injecting intravessel magnetite of nanoparticles, it is necessary to have not only reliable scientific dates about safety of recommended methodology to use nanoparticles, but also standardized water solution magnetite of nanoparticles with early studied and well-proven noninvasive physical and chemical properties.

Unfortunately, to date the advanced studies that would take into account it are absent. In the published advanced studies we met not a single reference to the use of the early studied standardized noninvasive forms magnetite of nanoparticles and methodologies of their application. Information about the mechanism of influence magnetite of nanoparticles on main biological systems of living organism including respiratory, cardiovascular, secretory, immune systems, cellular exchange is absent. Also we did not discover among the scientific publications of reliable dates about quantitative distribution magnetite of nanoparticles in organs and tissues after intravenous inject. Information about a mechanism of eliminate magnetite of nanoparticles from an organism is absent.

On the whole, aforesaid does not allow properly estimating the scientific and practicing significance early advanced studies which were published on theme to use magnetite of nanoparticles as contrasting means for MRI.

It was found in the choice of theme of the present investigation. The task was set in an experiment on animals to check possibility of the use of the before worked-out and studied methodology of intravenous inject of the standardized form water solution magnetite of nanoparticles (preparation of ICNB) [7-17] for contrasting of malignant tumour at MRI research.

The main purpose is to change the indexes of relaxation of T1 and T2 in area of malignant tumour during realization MRI by means of nanoparticles of ICNB.

II. MATERIALS AND METHODS

Investigations were performed on the males of rats of Vistar line, by age of 26-27 months. Rats lived in individual cages

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with standard ration of vivarium with free access to water and food.

One rat was relatively healthy. Others are with the present fibroadenoma of mammary gland. Wait of rates was identical. During investigations of animals we observed the principles of humanity, which expounded in declaration of Helsinki.

For 5 minutes prior to research intramuscular the rats get sedation. Subsequently control of MRI was carried out..

After the performed control of MRI, singly in a tail vein of the rat, from a calculation 0.6-0.8 ml/100 mg, 0.0225% was injected ICNB. The repeated was performed of MRI studies. Conditionally all MRI studies were divided into 4 stages:

Stage I is control (before intravenous inject of nanoparticles);

Stage II - in 5 minutes after inject magnetite of nanoparticles;

Stage III - in 24 hours after inject magnetite of nanoparticles;

Stage IV - in 96 hours after inject magnetite of nanoparticles.

Physical and chemical properties of ICNB:

- Osmolality theoretical of colloid solution is 500 mosm/l
- Size of magnetite of nanoparticles is 6-12 nm;
- Total area of surface magnetite of nanoparticles Ss = 800-1200 m^2/g;
- Magnetized of saturation is = 2.15 κA/m;
- ζ - potential = - 19 mV.

The investigations were performed on the MR-tomagraph Magneton Concerto of Siemens firm with power magnetic-field 0.2 T.

Got axial tomograms:

- T1 - the self-weighted sequences of Echo Spin of TR 50 ms, TE 17 ms the field of review a 250 mm, the thickness of cut 2 mm.

- T2 - the self-weighted sequences of Echo Gradient of TR 500 ms, TE 17 ms the field of review a 180 mm, the thickness of cut 4 mm.

The concentration of accumulation magnetite of nanoparticles was estimated by measuring brightness of image in a tumour and tissue of muscular of rats at MRI. The middle index brightness of image was accounted by measuring arbitrarily taken 8 points of minimum and maximal values of the investigated tissues. Got results were statistically processed by means of computer mathematical complex "Statgraf". The method of variation statistics comparison averages was used on the t-criterion of student.

III. RESULTS AND DISCUSSION

Before the beginning implementation of MRI was performed research of ICNB for the purpose of visualizing his contrast effect. In parallel of solution 0.9% NaCl was studied for comparison. Results MRI of research ICNB and solution of 0.9% NaCl were presented in Fig. 1.

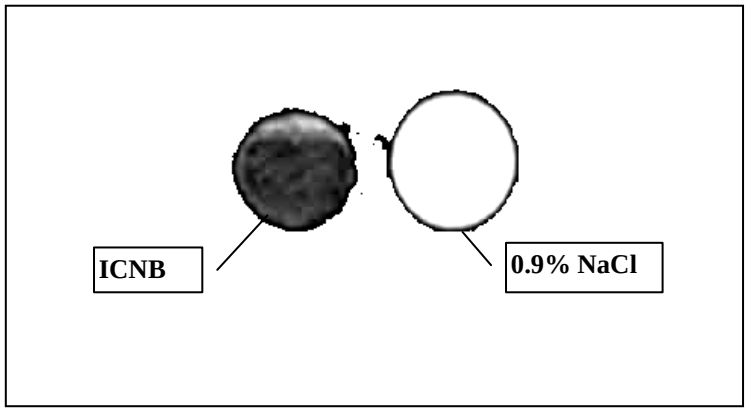

Fig.1. MRI research of ICNB and solution of 0.9% NaCl

The fig. 1 demonstrates the expressed contrasting effect of ICNB by comparing solution of 0.9% NaCl

Initially the protons of atom of hydrogen in preparation of ICNB are in the maximally structured state and have low index of relaxation. Therefore contrasting effect of ICNB at MRI is registered as darkening of image. This research confirmed

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possibility of the use of ICNB as contrasting means at MRI.

As a result of inject to the tail vein of rats preparation of ИКНБ at МРТ research an opposite effect is reliable. If Fig. 1 demonstrated the effect of darkening from ICNB at MRI, then after the intravenous inject of ICNB, opposite was exposed increase brightness of image in investigated tissues (Fig. 3).

Author's methodology the intravenous of inject allows to magnetite of nanoparticles of ICNB quickly dissolving in blood and in subsequent distributed in organs and tissues. Rapid dissolution of ICNB in blood prevents appearing rheological, microcirculation disorders and consequently the phenomena of hypoxia [6, 8].

Distributed nanoparticles of ICNB in tissues against a background of MR radiation strengthen influence of magnetic field on the protons of atom of hydrogen. The protons of atom of hydrogen alter the magnetic moment on opposite and then go back into initial position. As a result energy increases in nucleus atoms of hydrogen, time of relaxation of the excited protons grows. It registers oneself the system of tomograph. The comparative image of contrasting effect before and after inject of ICNB in rat with the fibroadenoma of mammary gland is presented in Figs. 2 and 3.

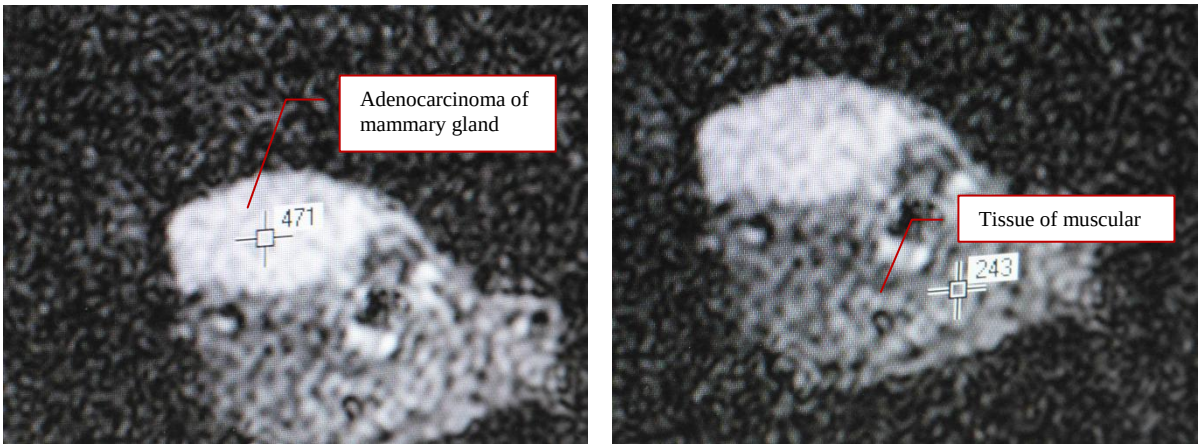

Fig. 2 Initial MRI study the brightness of image in rat with the fibroadenoma of mammary gland and tissue of muscular (471 conventional sign – tumour; 243 conventional sign – tissue of muscular)

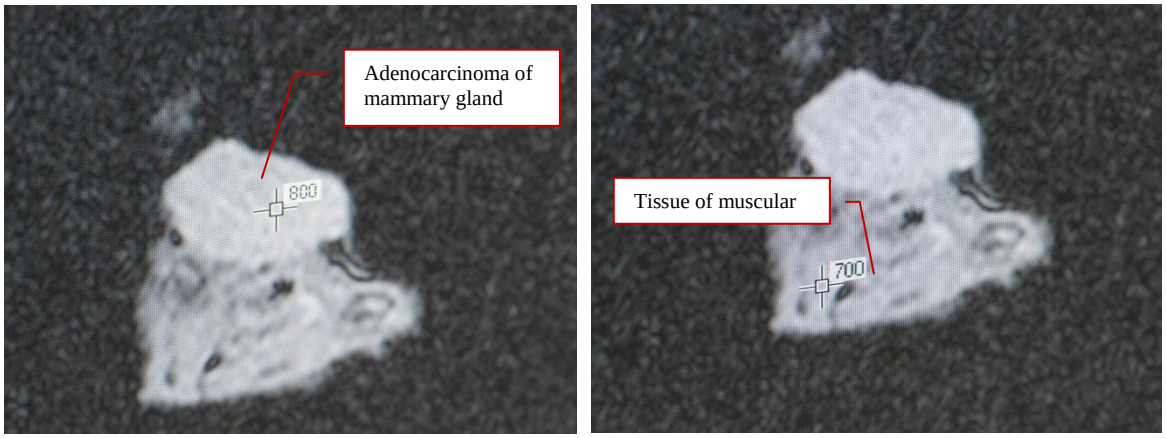

Fig. 3 MRI study the brightness of image rat with the fibroadenoma of mammary gland and tissue of muscular on the first minutes after intravenous inject of ICNB (800 conventional sign - tumour; 700 conventional sign - tissue of muscular)

Figs. 2 and 3 in comparison show evidently that already on the first minutes after the intravenous inject nanoparticles of ICNB at MRI the parameters of relaxation T1 and T2 change and reliable ($p<0.001$) a contrasting effect increase in like brightness of image in the investigated tissues. So, after inject of ICNB in tumour of tissue the index of brightness of image increased on the average on 329 ± 12 conventional sign and was 800 ± 12 conventional sign ($p<0,001$), but in muscular – on 457 ± 12 conventional sign and was 700 ± 12 conventional sign ($p<0,001$).

It should be noted that registering the low parameters of relaxation is possible only in case of high concentration magnetite of nanoparticles in blood and tissues. However, the high concentration of nanoparticles in blood stream is potentially dangerous for living organism, because it causes the origin of hypoxia in tissues. Especially this is very significant for organs: brain, heart, liver, lungs, and kidneys.

Thus, taking into account foregoing, application magnetite of nanoparicles as contrasting means at MRI in the safe variant of methodology is practically not possible. This experiment showed that using nanoparticles of ICNB in certain methodology

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can not be independent contrasting means at MRI. Worked out methodology of intravenous inject nanoparticles of ICNB on a background of MR of radiation in it safe variant only for certain ($p<0.001$) strengthens the brightness of image of tissues. Dynamic change of indexes brightness image in tumour and muscular tissues in a sick rat after intravenous inject of ICNB is presented in Fig. 4. Dynamic change of indexes brightness image in muscular tissues in both rats groups after intravenous inject of ICNB is presented in Fig. 5.

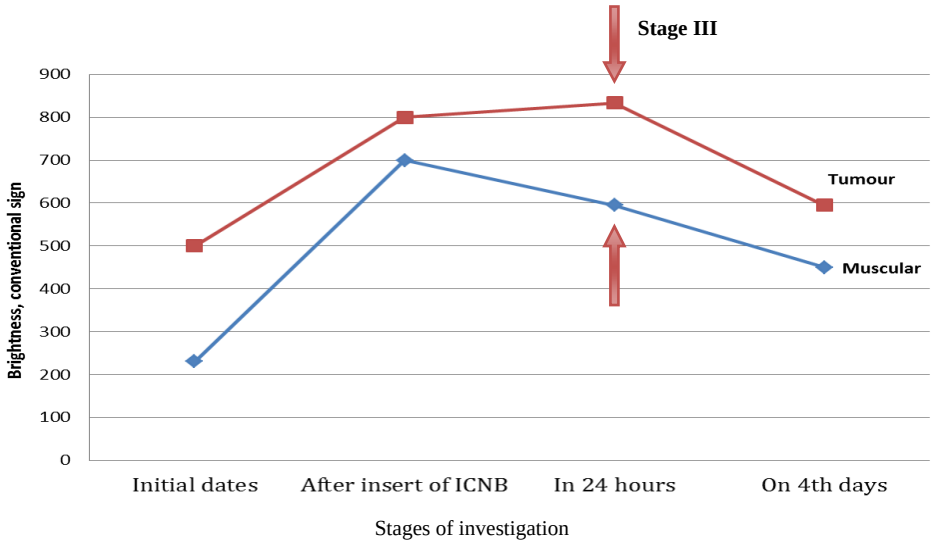

Fig. 4 Dynamic change of indexes brightness image in tumour and muscular tissues in a sick rat after intravenous inject of ICNB on various stages at MRI investigation (M±m; n=8)

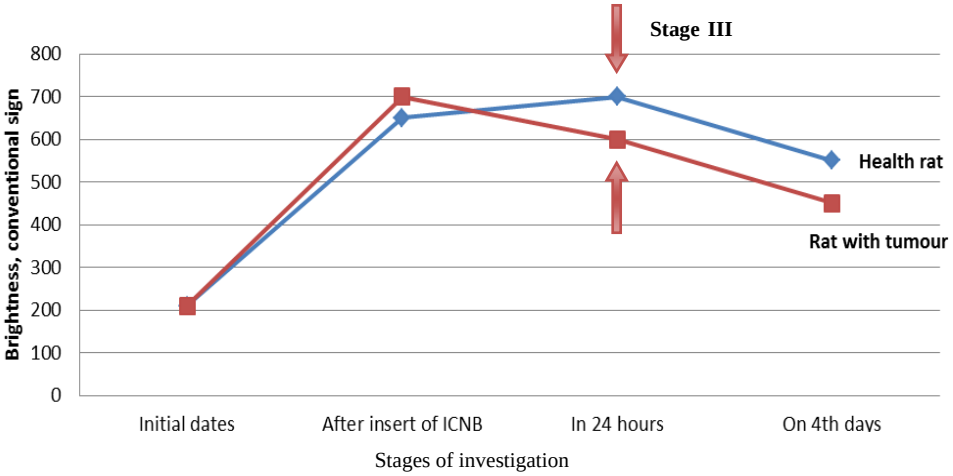

Fig. 5 Dynamic change of indexes brightness image in muscular tissues in both rats groups after intravenous inject of ICNB on various stages at MRI investigation (M±m; n=8)

Opposite, in health rat on stage III investigation was reliable ($p<0.001$) revealed maximally increasing brightness of image in muscular tissue (700±19 conventional sing). Change of brightness image on stage III investigation in muscular tissue is caused by less accumulation in muscular tissue nanoparticles of ICNB in rat with tumour than in muscular tissue in health rat. This effect is explained as the following:

1. The surface of malignant tumour cells as compared to healthy has higher negative charge, because nanoparticles of ICNB are selectively accumulated in malignant tumour tissue.

2. Weak contact between cells of malignant tumour is reason for elevating accumulating nanoparticles of ICNB in intercellular space and rising of time of their elimination.

IV. CONCLUSIONS

In an experiment it is shown on rats that biocompatible standardized nanoparticles of ICNB can be effectively used at MRI. It is well-proven that nanoparticles of ICNB for certain ($p<0.001$) strengthen a contrasting effect at MRI.

Methodology of safe intravenous application of ICNB is excluding the use of magnetite of nanoparticles in the variant of independent contrasting means at MRI.

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On the mechanism of action the nanoparticles of ICNB cause the convertible changes which is reason for the temporal increase of mobility of protons of hydrogen in near cell liquid. It inevitably modifies the metabolic process in malignant cells that in perspective has hope in elaborating new ways of the target therapy of malignant neoplasm.

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Andrey Belousov was born in 1965 in Ukraine.

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