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Original research article

Biodegradable seeds of holmium don't change neurological function after implant in brain of rats

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ABSTRACT

Aim: To evaluate the surgical procedure and parenchymal abnormalities related to implantation of ceramic seeds with holmium-165 in rats' brain.
Background: An effective method of cancer treatment is brachytherapy in which radioactive seeds are implanted in the tumor, generating a high local dose of ionizing radiation that can eliminate tumor cells while protecting the surrounding healthy tissue. Biodegradable Ho^{166}-ceramic-seeds have been addressed recently.
Methods and materials: The experiments in this study were approved by the Ethics Committee on Animal Use at the Federal University of Ouro Preto, protocol number 2012/034. Twenty-one adult Fischer rats were divided into Naive Group, Sham Group and Group for seed implants (ISH). Surgical procedures for implantation of biodegradable seeds were done and 30 days after the implant radiographic examination and biopsy of the brain were performed. Neurological assays were also accomplished to exclude any injury resulting from either surgery or implantation of the seeds.
Results: Radiographic examination confirmed the location of the seeds in the brain. Neurological assays showed animals with regular spontaneous activity. The histological analysis showed an increase of inflammatory cells in the brain of the ISH group. Electron microscopy evidenced cytoplasmic organelles to be unchanged. Biochemical analyzes indicate

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there was neither oxidative stress nor oxidative damage in the ISH brain. CAT activity showed no difference between the groups as well as lipid peroxidation measured by TBARS. *Conclusions:* The analysis of the data pointed out that the performed procedure is safe as no animal showed alterations of the neurological parameters and the seeds did not promote histological architectural changes in the brain tissue.

1. Background

Tumors of the central nervous system are a medical challenge, particularly those of rapid progression, such as glioblastoma multiform, and brain metastasis.[2] Recent scientific advances in diagnosis and disease control have not yet been sufficient to provide a cure for cancer, although remission occurs in many cases.[3] Thus, the search for new treatment modalities is still required.[4–6]

Brachytherapy is an efficient method for cancer treatment,[7] deploying discreet radioactive segments (seeds) in the tumor and generating a high local radiation dose, which is able to eliminate tumor cells while preserving the healthy surrounding tissue. The potential of this therapy justifies the development of new procedures of radioactive implants in tumors.[4,8,9]

Implants made of bioactive materials have been used in medicine and dentistry since the 1990s.[10] The mechanism by which the tissue connects to the implanted material is directly related to the tissue response, the implant interface and the topography of the material.[11] Resorbable implants are designed to gradually degrade with time and be replaced by local tissue, thus reducing the likelihood of side effects on the organism.[12,13]

Bioactive radioactive seeds are a new concept.[3–5,13,14] Ceramic seeds incorporating Sm-152 and Ho-165 isotopes were processed by the sol-gel method.[14] After neutron exposure, the radionuclides Sm-153 or Ho-166 are activated in the ceramic seeds. Those nuclides will decay by emission of high-energy β particles along with γ radiation of 103 keV from Sm-153 and 80 keV from Ho-166, with half-lives of 46.3 h and 26.8 h, respectively.[4,15] Radioactive seeds implanted into tumors of the central nervous system will deposit high doses near the implant, turning in stable isotopes after 8–10 half-lives, i.e. nearly a week, transforming it into a cold material. After cancer cells elimination, the surrounding health tissues will be in contact and interact with such ceramic material during a long-term period. Therefore, short half-life radioactive seeds provide a quick, weeklong brachytherapy followed by a long-term non-radioactive tissue interaction. In this stage, the safety and the toxicity of the cold Ho-165 ceramic seeds in the central nervous system is unknown and may bring some concerns.

2. Aim

Investigations regarding the interaction of cold ceramic seeds with holmium-165 and their effect on the parenchyma of the brain tissue that hold seed implants are not understood. The aim of this study was to investigate the safety of the procedure of the ceramic seed implants with holmium-165 in the central nervous system. Therefore, the surgical procedure and parenchymal abnormalities related to implantation of ceramic seeds with holmium-165 in rats' brain will be investigated.

3. Materials and methods

3.1. Animals

Animal care and experimental procedures were approved by the Ethics Committee on Animal Use (CEUA) at the Federal University of Ouro Preto (UFOP), under protocol number 2012/034, and followed the rules established by the Brazilian Society of Laboratory Animal Science (SBCAL). During all experiments, the animals were kept at room temperature ($21 \pm 2\,^{\circ}C$) and under controlled light cycles in a vivarium at the School of Nutrition (UFOP), with food and drinking water *ad libitum*. Twenty-one adult Fischer rats were divided into Naive Group – 7 Fischer rats that received no surgery, Sham Group – 7 Fischer rats that underwent the surgical procedure without implantation of seeds, and Group with implantation of seeds of Holmium (ISH) – 7 Fischer rats that were subjected to the surgical procedure and the implantation of seeds. 30 days after the animals underwent surgery for implantation of holmium seeds in the brains, radiographic examination was performed. Later, the animals were euthanized by an overdose of anesthetics – sodium pentobarbital, 100 mg kg^{-1}, their intramuscular and brain tissues were collected for analysis.

3.2. Bioactive micro-seeds

Inactive Ho-165 micro-seeds were processed by the sol-gel method following the proposed protocol.[13] The entire process was laboriously accomplished in vacuum, eliminating inherent defects in the seed. After mixing the reagents, the solute-filled molds were prepared to produce micro-seeds of 1.6 mm length and 0.5 mm diameter. Many methods for production of molds were used in an attempt to obtain the smallest seed of acceptable size for the interstitial brachytherapy implant. The vacuum preparation was necessary to avoid formation of bubbles and to allow the fluid to fill the micro holes of the mold. The gelation process, aging, and thermal treatment were accomplished in agreement with methods described in the scientific literature.[10]