

The Surgical Viability and Radiological Monitoring of Brain Implants of Bioactive Micro-Seeds in an Animal Model

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ABSTRACT

The interstitial implant is a therapeutic modality in brachytherapy of the head and neck. Presently, the seeds implanted in tumors in the central nervous system are metallic I-125. After the full emission of the radionuclide, the seed remains inert in the implanted area. Bioactive ceramic seeds have been prepared for this research group incorporating Sm-152 to be active in Sm-153. The main goal of the present study is the development of a the surgical technique for implanting the biodegradable radioactive micro-seeds in the brains of rabbits, as well as the observation of the clinical reactions of the animal after implantation of two sets of three seeds. The surgical procedure consisted of performing two separate perforations 10 mm from each other in the skull, permitting the implantation of two groups of three seeds, totaling six seeds. The results of the pilot study showed the effectiveness of the surgical procedure and of the biocompatibility of the seeds and the lack of presence of adverse reactions, functional sequels, or inflammation in a follow up 50 days post-surgery. Such seeds of reduced volume, 0.2 x 1.6 mm, could be monitored by computerized tomography 30 days after implanting.

Key words: Brain Implant, surgery, bioactive seeds, Sm-153.

INTRODUCTION

The interstitial implant can be temporary or permanent. The main indications for the temporary interstitial implant are for healing accessible tumors on skin, neck, tongue, tonsils, mouth floor, lips and extremities. The intra-thoracic and intra-abdominal permanent interstitial implant is indicated for organs such as the lung, pancreas, bladder, prostate and SNC (Salvajoli, 1999). The implants are accomplished with needles used as guides for placing radioactive material in the appropriate position, covering of absorbed dose all implanted volumes. The needles are usually made of stainless steel and are available in several

lengths. The diameter varies according to the purpose of the application and the size of the radioactive material. Breast tumors and head and neck tumors are examples of organs that can be reach with this type of implant.

Currently, the brachytherapy technique applies seeds or metallic radioactive lines made of Pd-103, Cs-137, Ir-192 and I-125, the last having 59.4 days of half-life. The I-125 seed implants are often applied in interstitial brachytherapy to tumors in the central nervous system (CNS) and in the prostate. The idea of bioactive and biodegradable seeds, in substitution of metallic seeds, is attractive mainly because of the hypothesis that the degradation of the strange body promotes a

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possible functional recovery of the irradiated area, reducing the fibroses rate. However, a smaller volume of seeds with larger specific activity will also be able to influence in this process.

According to Martinez and collaborators. (1990), the treatment of recurrent cancer of the previously irradiated head and neck represents a complex situation because of the fibroses present and the poor vascularization of the tissues. In this clinical case, the permanent biodegradable implant can provide a favorable clinical repercussion. Also according to Martinez and col. (1990), the interstitial irradiation is often used in initial or advanced primary head and neck tumors. However, it can also be used in treating cancer previously treated by external radiotherapy. The precision of placing the seeds and monitoring the implants can be achieved through ecography (ultrasound), radioscopy (fluoroscopy) or computerized tomography. According Martinez and col. (1990), the main goal in the treatment of tumors of the head and neck with brachytherapy should be the minimization of the surgical morbidity, the reduction of the functionality and later deleterious effects. According to Salvajoli (1999), Rn-222, Au-198, I-125 and Pd-103 are isotopes that have been used in permanent implants for the treatment of tumors in several clinical locations.

Early research has been developed with the intention of manufacturing biodegradable and biocompatible radioactive seeds. Bioactive glass has been used for cancer treatment through sol-gel processing incorporating Sm-153 (Roberto, Pereira, Campos, 2004) or through the elaboration of radioactive gels incorporating Re-188 and Ho-166 (Mendes, Campos, 2004). Both processes seek the refinement of the existing techniques.

The present article addresses the surgical viability of CNS implants using manufactured micro-seeds prepared in-house in the rabbit brain. The goal of this work consisted of verifying the clinical symptoms related with the non-radioactive seed implant and of evaluating the surgical procedure and the radiological monitoring before initiating the implantation of radioactive Sm-153 seeds. This radioisotope has a half-life of 46.27 hours, is a beta emitter and emits 103 keV gamma rays, among others; and it may be an alternative to the I-125 because it produces a larger dose rate than I-125. Mendes and Campos (2004) had accomplished dosimetric studies considering distribution of M-HAP macro-aggregates on

interstitial implants into the brain, comparing dosimetric M-HAP seed implants with metallic I-125 seeds. The Radial Dose Profile (RDP) for a unit of 30 mm radioactive segments was assessed, relating the dose-rate with radioisotope type. The distribution of a three-dimensional absorbed dose was presented for a selected configuration of Re-188-HAP and I-125 in an anthropomorphic and anthropometrical human phantom. The present article presents a refinement of protocols in search of the best way to perform surgery and monitor the bioactive micro-seeds in the brain using an animal model.

MATERIALS AND METHODS

Inactive Sm-152 micro-seeds were processed by the sol-gel method following the proposed protocol (Roberto, Pereira and Campos, 2003, 2004); however, variations were addressed in the concentrations of calcium and samarium, as well as in the temperature rates. The entire process was laboriously accomplished in vacuum, eliminating inherent defects in the seed. After mixing the reagents, the solute-filled molds were prepared for producing micro-seeds in the small 0.2 x 1.6 mm size. Many methods of producing molds were experimented 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 literature (Hench, 1990).

Surgical procedure

Surgical equipment. The following set was used: an operating table, fluorescent lamp with adjustable focus, autoclave for sterilization of the surgical instruments, instrumentation table, oxygen-therapy system and vacuum

Surgical Material. The surgical material consisted of operating fields, compresses and gauzes. In each operation, a cable of bistoury number 4; a sheet of bistoury number 15; a 14-cm door-needle; a 12-cm, anatomical tweezers; a 12-cm, toothed tweezers; a 17-cm, curved scissors with a romba tip; a fine-tipped straight scissors.

Depilation and asepsis. The depilation was performed by a permanent type of shaving with disposable sheets. In the antiseptics, a 70% alcohol solution and a straight, toothed, homeostatic tweezers were used to hold the wet gauze for the antiseptic.

Anesthetic pharmacy. As central anesthetics and dissociation, injectable xilasina solution, together with an injectable solution containing 50 mg/cm³ of S-(+)-ketamina hydrochloride, were applied. Nylon 4-0 holed threads were used for Suture thread.

Subject of experimentation. The experimental model was developed in New Zealand rabbits. The animals were treated according to the Law no. 6.638, of May 08, 1979; Decree n. 24.645 of July 10, 1934, and the international principles of good animal treatment, according to the literature and in agreement with the ethical principles of the Brazilian School of Animal Experimentation (COEP).

Preoperative and anesthesia. After the contention of the rabbit, the same was positioned in ventral decubitus on the operating table. Intramuscular infusion of 2% xilazina (5 mg/kg) in the right gluteal area had sedative, analgesic and muscular relaxation effects. The infusion of 50 mg/kg dose of S-(+)-ketamina hydrochloride was performed intramuscularly in the left gluteal area. Partial depilation of the scalp of the calvaria, after skull palpation, following antiseptics with 70% alcohol solution, was accomplished.

Operative acting. After the placement of field surgical with holes, the incision in the scalp of the calvaria of the animal, longitudinal medium, of approximately 2.0 cm in length, was made. Opening for plans, with incision of the skin and

subcutaneous, incision of the galea aponeurotic and woven slack subaponeurotic, longitudinally.

Following the permanent interstitial implant, double-tipped hypodermic needles were used as guides for the positioning of the micro-seeds in the brain. The procedure involved the trepanation of the parietal left bone, up to 3 mm, laterally from the medium level of the sagittal suture, with drill number 1.5. The introduction of 7 mm of a G6 hypodermic puncture needle loaded with the three biodegradable seeds was accomplished, and the injection of the seeds into the brain mass followed. The procedure was repeated, with another trepanation 3 mm laterally and 10 mm behind the first.

The layers of the incision were sutured with three simple stitches with 4-0 nylon thread. The liberation of the animal was followed for operative recovery in an individual cage, with a diet of water and ration.

Radiological monitoring

Thirty days after the implants, the animal was contained and anesthetized, and a computerized tomography (CT) was performed. The anesthesia was applied in the superior area of the inferior member, following the procedure described previously. The medium duration of CT was 15 minutes.

Imaging. The tomographic imaging was performed at MEDIMAGEM/Sete Lagoas, presetting the window for the brain technique, in GE equipment, with 2 mm spacing in the field placed under the rabbit's brain. The images were enlarged and printed.

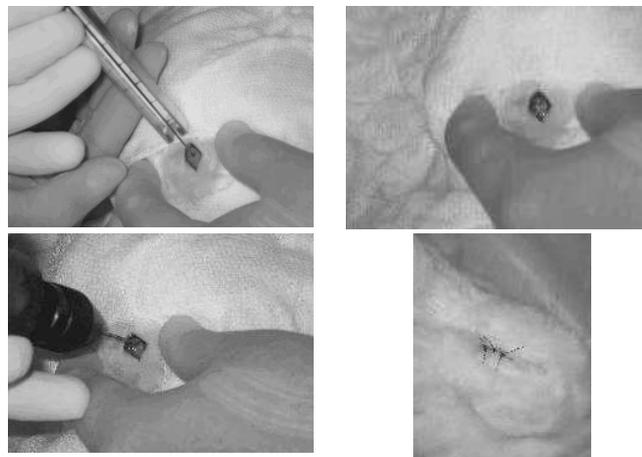


Figure 2 - Perforation of the skull of the rabbit, implant of the seeds and closing with stitches.



Figure 3 - CT of the brain of the rabbit, indicating the implant location

RESULTS AND DISCUSSION

The perforation of the skull, as well as a micro-seed in the brain, taken in a computerized tomographic image, is shown in Fig. 2. The number of seeds implanted was six units, but the plane of the implants and the tomographic plane did not match and the seeds appeared as one. No hematoma or inflammation was observed in the images. The rabbit that received the micro-seed implants did not present signs of behavioral, motor or functional alterations.

CONCLUSION

The result obtained in this study led to the conclusion that the surgical procedure is viable, without observable deleterious effects on the animal. The follow-up at 30 days did not indicate any clinical alteration. The surgical procedure for implanting the micro-seeds is acceptable for application applied in brain tumors, specifically without manifestation of sequels, such as hematomas, fibroses and functional losses.

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RESUMO

Os implantes intersticiais podem ser utilizados em braquiterapia de cabeça e pescoço. Atualmente as sementes implantadas no CNS são de I-125 metálicas. Após o decaimento do radioisótopo, a semente fica inerte na região implantada. Sementes cerâmicas bioativas tem sido preparadas pelo grupo de pesquisa incorporando Sm-152. O presente estudo tem o objetivo de viabilizar a técnica cirúrgica de implantes de microsementes biodegradáveis não radioativas no cérebro de coelhos, bem como verificar as reações clínicas e funcionais do animal ao corpo estranho implantado. O procedimento cirúrgico compreendeu em proceder duas perfurações separadas em 10mm na calota craniana onde foi possível a implantação de dois conjuntos de três sementes, totalizando seis sementes. Os resultados do estudo piloto evidenciam a eficácia do procedimento cirúrgico e do material implantado, já que não foram encontradas

reações adversas, seqüelas funcionais, ou resposta inflamatória durante 30 dias pós-cirurgia. Tais sementes de reduzido volume, 0.2x1.6mm, puderam ser monitoradas por tomografia computadorizada.

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