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LOCAL ADJUVANTS IN SURGICAL MANAGEMENT OF BONE METASTASES

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Curettage is one of the most common method for surgical treatment of bone metastasis. Local adjuvant improve most commonly used for improving the effect of curettage in local cancer surgery may exerted their effects either chemically either physically; in Orthopedic Oncology the most common are phenol, liquid nitrogen, laser, and cement. This article reviewed the main characteristics of the most common chemical and physical agents used in bone oncology, emphasizing the toxic effects of some of them, especially phenol and liquid nitrogen.

BACKGROUND

Local adjuvants play an important role in surgical treatment of metastatic lesions of the skeleton. What determines the choice of the adjuvant is generally the surgeon's personal experience. The use of these substances is aimed at extending the results surgically obtained by curettage through the elimination of any remaining neoplastic cells. Their utilization has led to a significant reduction in the percentage of local recurrences.

At the beginning of the 1970s the first local adjuvant used in orthopedic oncology surgery was liquid nitrogen cryotherapy, developed by Marcove at Memorial Sloan-Kettering of New York, and PMMA cementation, described for the first time by Persson and Wouters. Over time other local adjuvants have been used. These are both chemical, such as phenol, ethanol and H_20_2, and physical, such as thermo-ablation with electro-scalpel, and above all Argon-based thermo-ablation and cryosurgery with Cryoprobes.

It is essential to highlight that any physical or chemical agent used as an adjuvant cannot correct a badly performed curettage. In fact, it has to be done aggressively by using high-speed drill and by eliminating the residual material left by burr drilling. This is crucial to the oncological success of the surgical procedure.

LIQUID NITROGEN

Cryosurgery is the therapeutic use of extreme cold to induce tissue necrosis with ablative intent. Modern cryotherapy was born in 1963 in the treatment of Parkinson's disease (1). In 1966 Cage et al. (2) demonstrated the results of cryotherapy on the bones of a canine model. The use of liquid nitrogen stored at -197° in the treatment of bone lesions was introduced by Marcove in 1973 (3). The advantages of this method are a high rate of efficacy, the preservation of adjacent articulations and the possibility of avoiding excessive reconstruction by prosthetic replacement or transplants. The risks are a possible necrosis of the adjacent soft tissue, neuropraxia of the near nerve structure and risk of fracture (5-25%) (4-5-6).

In order to emphasize the rationale of the method, we need to consider what happens to a cell at such low temperatures: thermal shock, intracellular dehydration and toxic electrical imbalance, the formation of ice crystals (which is due to rapid freezing and causes direct cell death), the disruption of the cell membrane and microvascular alterations (which occur during a slow thaw and cause secondary and progressive cell death). Also a freeze-thaw cycle causes these crystals to coalesce and mechanically disrupts the cell membrane, causing cell death. Cellular necrosis occurs at temperatures varying between -21° and -60°, beyond which the percentage of necrosis does not increase. Tissues do not respond to cryotherapy in the same way: their response depends on cell typology, density, tissue vascularization, the presence of cryoprotective molecules, the number of freeze-thaw

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cycles and the absolute temperature reached in the process and duration of freezing (7).

From a technical point of view, the golden rule in the procedure described by Marcove is the following: allowing wide retraction and protection of soft tissue and nerve vascular structure, a tourniquet, aggressive motorized curettage of the tumor with the creation of a large bone window, pouring the cryogenic agent through a funnel (after curettage liquid nitrogen is poured into the tumor cavity through a funnel sealed at the base with Gelfoam. The first pouring of liquid nitrogen lasts only 2 minutes to allow the Gelfoam to freeze and completely seal the system); monitoring the temperature of soft tissues with thermocouples; freeze-thaw cycles (the tissue has to be frozen up to -40° for 5 minutes, thaw is then allowed to occur and once a temperature of 0° is reached another freeze-thaw cycle is administered, in fact it has been recognized that after the first cycle the conductivity of the cold temperatures increases). If a physis is still open, only one cycle should be administered; irrigating the cavity with saline solution; intra-articular monitoring with thermocouples; reconstruction of soft tissues; reconstruction with PMMA and internal fixation (to provide immediate stability, structural support and allow early rehabilitation of the adjacent joint); postoperative prophylactic antibiotics. Weight-bearing is not allowed for six weeks.

The cytotoxic efficacy of cryosurgery has a range of 7–12-mm with no effect on articular cartilage. A rate of 5-25% of fractures of the part treated with cryosurgery is one of the most common complications related to this technique (5-6). This is due to trabecular necrosis with the interruption of osteoid matrix and extensive bone marrow necrosis with minimal inflammation and subsequent liquefaction with progressive fibrosis. The ossification of the cryonecrotized bone tissue, which behaves as an acellular graft, is slow. Therefore, cryosurgery can be defined as a biological intra-compartmental resection allowing a wide excision in situ but without the morbidity of massive resection and disarticulation. Cryoprobes are an evolution within the field of cryosurgery. In this system the application of low temperatures is achieved through local conduction and not through instillation, using Argon at -190° as freezing agent and Helium at 35° as thawing agent. Some systems use only Argon as by regulating Argon gas pressure its temperature can be determined using the Joule-Thompson effect with the aid of computerized systems. The advantages of this methodology include reaching a more rapid freezing temperature compared to the system using liquid nitrogen and a more effective control of the temperature achieved. This system, however, has its limits in the number, diameter and cost of each cryoprobe, the volume of pressurized Argon, the time needed to administer repetitive freeze-thaw cycle, to the point where major bone cavities are treated more rapidly and more cheaply with liquid nitrogen following Marcove's technique (8) while cryoprobes are used to treat smaller lesions. In this case, as there is no need to isolate the funnel, the physiological solution is utilized both as a thermal conductor, to conduct the cold into the lesion only up to its rim and not beyond (to avoid contact with adjacent tissues) and as thermo-modelling to irrigate and protect the adjacent tissues by making any frozen residual part of the physiological solution itself melt. A viscous jelly utilized in urology and gynecology can be used as an alternative to physiological solution (Surgilube) (9). The steps following cryoprobe technique are identical to those of traditional cryosurgery (10).

ACRYLIC CEMENT PMMA

A temperature between 42° e 47° is sufficient to destroy gonadal, embryonic, blood cartilaginous and neoplastic cells. Charnley had demonstrated that an acrylic cement mass of the size of a golf ball could reach the temperature of 90° (11), then in 1976 Persson and Wouters introduced the use of PMMA-based cement into the treatment of bone lesions (12). The rationale of this method lies in preserving the skeletal segment, in the efficacy of local control, rapid recovery of weight-bearing ability, easy recognizing of a local recurrence while still having the possibility of other therapies (13).

It was assumed that PMMA induces perilesional tissue necrosis by means of the heat produced by the exothermic polymerization of the compound and a possible toxic effect of the monomer itself. Experimental studies, however, have demonstrated that the thermal necrosis of the bone is induced within a temperature range of 48°-60° and it is variable and time-dependent, while the maximum temperature of the bone/cement interface reached in an experimental model was 46°. The latter was reached in a condition, as it is mass and form dependent (14), in which the temperature of the nucleus of the mass cement increases depending on the size of the mass itself. Furthermore, the speed of heat dissipation depends on the bone vascularization, which is why the effect is greater if the blood flow is interrupted by a tourniquet application. In the end an evident cellular toxic effect of the methyl methacrylate monomer does not exist (15). The efficacy of the cement is within the range of 1,5-2 mm of the spongy bone and 0,5 of the cortical bone (16). It is noteworthy that cement is utilized not only as filler but also as material to reinforce an intramedullary fixation such as a locked nail. In these cases it is useful to choose the nail of the largest caliber possible, perform reaming at least 2 mm beyond the chosen diameter and try reducing the fracture before

the introduction of cement. The cement chosen among those available has to be low-viscosity cement which has to be cooled to slow down the speed of polymerization and then introduced into the whole diaphysis in case of permeating bone lesions. After the cementation of the canal the locked intramedullary nail is inserted in static mode. Instead, in localized lesions cement has to fill the space left by curettage and the osteosynthesis device has to be fixed on it (17).

CEMENT ADDED WITH ANTIBLASTICS

In this method anticancer drugs are mixed with PMMA to utilize a slow release effect from within the cement. The most commonly used drugs are methotrexate, used aspecifically, cisplatin for lung tumors and doxorubicin for breast cancer (18). In a recent Italian study Rosa, Maccauro et al. (19) demonstrated that with this technique anticancer drugs are released in an active form from the cement with the passage of time. They tend to form granules and each drug conserves its own cytotoxic characteristics with a different effect on the cell vitality of the related culture. Even if the study has not clarified yet whether the drug is released only by the cell culture/drug-loaded cement interface, it has positively confirmed present data in medical literature showing that the heat induced by polymerization does not affect the pharmacodynamic features of these drugs (20).

PHENOL

Phenol, also called phenolic acid, is a bacteriostatic compound in a concentration of 0,1-1%, bactericide above 1%, cytotoxic and non selective in concentrations higher than 3% and local anesthetics in concentration higher than 5% (21). Phenol acts through denaturation of cellular proteins which determine cell permeability up to the actual destruction of the cells. It can destroy about 1-1,5mm of tumor tissue through coagulative necrosis. Phenol is produced also physiologically by the natural destruction of aromatic amino acids in the intestine and is normally excreted via the kidney through urine metabolites. The normal concentration of phenol in the human body is 0,1 mg/l and the maximum urine concentration allowed in a working environment is of 300 mg/l urine. It exerts harmful effects on the function of the heart, lungs, kidneys and the nervous system. The use of phenol is selectively indicated for cartilage tumors, in a concentration of 5% at ambient temperature and either is directly poured into the tumor cavity or applied to the cavity surface with a tampon. It is important to wash the cavity before phenol instillation in order to remove any tissue debris or clots, being extremely careful not to damage and/or irrigate the periskeletal soft tissue. This procedure has to be repeated three times, irrigating wall clots and avoiding marginal dilution of arrival blood in order to cover the inner wall of the cavity homogeneously. The amount of phenol needed has to be left in situ for 60 sec., then it has to be removed through a physiological solution wash. Other authors, however, use phenol concentrations of 90% which is left in situ for 5 minutes and then washed with physiological solution (22). The physiological solution has replaced both the 70% alcohol irrigation, because it is highly toxic and phenol is easily soluble in water in concentrations of 5%, and the irrigation with hydrogen carbonate solution (23). Phenol is used associated with PMMA. Trieb et al. (24) report that recurrences are not linked to the treatment of cancer with or without adjuvant phenol therapy, but rather to a well done curettage, while Capanna et al. (25) describe a recurrence rate of 41% in cancers treated without phenol compared to the 7% of those ones treated with phenol out of 165 different benign tumors with a recurrence potential.

ELECTRIC CURRENT

Electro-scalpel cauterization has a general cytotoxic effect in a range of 1mm. In this case a radio frequency electric current is directly applied to the tissue to perform cauterization and control bleeding. The efficacy of this technique is enhanced if it is performed with an Argon beam. In this technique, developed within the field of laparoscopy, an argon beam is used to conduct electric current to the tissue. Electric current in the form of ionized argon gas has an ionizing power inferior to that of oxygen and also can enhance the procedure effect by physically removing blood and other lesion tissues, thus allowing higher visibility during surgery. As described in experimental studies, its medium efficacy reaches a depth of 2,4 mm, while the application time is 10 seconds for each bone portion to be treated, with regulated power at 100 W (26-27). Argon coagulation results in tissue vaporization, carbonization and coagulative necrosis, dependent on width, power and time. Tissue desiccation causes tissue carbonization, thus the cavity tends to assume a characteristic dark coloring. As data in medical literature confirm, this technique is easier to manage than others.

REFERENCES

1. Cooper IS. Cryogenic surgery: a new method of destruction or extirpation of benign or malignant tissues. N Engl J Med 1963;268:743-9.
2. Gage AA, Green GW Jr, Neiders ME, Emmings FG. Freezing bone without excision. An experimental study

of bone cell destruction and manner of regrowth in dogs. JAMA 1966;196 (9):770-74.

3. Marcove RC, Lyden JP, Huvos AG, Bullough PB. Giant-cell tumors treated by cryosurgery. A report of twenty-five cases. J Bone Joint Surg Am 1973;55 (8):1633-44.
4. Ippolito V, Motta C. Advantages of surgical treatment of metastatic bone disease. Acta Oncologica 1989;10 (1):45-52.
5. Malawer MM, Bickels J, Meller I et al. Cryosurgery in the treatment of giant cell tumor. Along-term followup study. Clin Orthop Relat Res 1999;359:176-188.
6. Marcove RC, Weis LD, Vaghaiwalla MR et al. Cryosurgery in the treatment of giant cell tumors of bone. A report of 52 consecutive cases. Cancer 1978; 41(3):957-969.
7. Bickels J, Meller I, Shmookler BM, Malawer MM. The role and biology of cryosurgery in the treatment of bone tumors. A review. Acta Orthop Scand 1999;70(3):308-15.
8. Marcove RC, Miller TR. Treatment of primary and metastatic bone tumors by cryosurgery. JAMA 1969;207 (10): 1890-94.
9. Bickels J, Kollender Y et al. Closed argon-based cryoablation of bone tumors. J Bone Joint Surg Br 2004; 86(5):714-8.
10. Henshaw RM. Treatment of bone lesions with cryoprobes. Techn Orthop 2007; 22(2):134-142.
11. Charnley J. Acrylic Cement in Orthopaedic Surgery. Brit Med J 1970;15:73-74.
12. Persson BM, Wouters HV. Curettage and acrylic fixation cementation in surgery of Giant cell tumor of bone. J Bone Joint Surg 1976;120B:125.
13. Malawer MM , Dunham W. Cryosurgery and acrylic cementation as surgical adjuncts in the treatment of aggressive (benign) bone tumors. Analysis of 25 patients below the age of 21. Clin Orthop Rela Res1991;262:42-57.
14. Leeson MC, Lippitt SB. Thermal aspects of the use of polymethylmethacrylate in large metaphyseal defects in bone. A clinical review and laboratory study. Clin Orthop Relat Res 1993; 295:239-245.
15. Malawer NM, Marks MR et al. The effect of cryosurgery and polymethylmethacrylate in dogs with experimental bone defects comparable to tumor defects. Clin Orthop Relat Res 1988;226:299-310.
16. Mjoberg B, Pettersson H, Rosenqvist R, Rydholm A. Bone cement, thermal injury and the radiolucent zone. Acta Othop Scand 1984;55:597-600.
17. Capanna R et al. Indicazioni e strategia chirurgica nelle metastasi ossee da carcinoma delle estremità e dei cingoli pelvico e scapolare. Corso di Istruzione SIOT, 2000
18. Hernigou P, Thiery JP, Benoit J et al. Methotrexate diffusion from acrylic cement. Local chemotherapy for bone tumours. J Bone Joint Surg Br 1989;71(5):804-11.
19. Rosa MA, Maccauro G, Sgambato A, Ardito R., Falcone G, De Santis V, Muratori F. Acrylic cement added with antiblastics in the treatment of bone metastases. Journal of Bone and Joint Surgery - British Volume, Vol 85-B, Issue 5.
20. Greco F et al. Polymethylmethacrylate-antiblastic drug compounds: an in vitro study assessing the cytotoxic effect in cancer cell lines: a new method for local chemotherapy of bone metastasis. Orthopaedics 1992;15:189-94.
21. Reynolds JEF. The extra pharmacopoeia, 30th edn. The Phamaceutical press:570-572, London 1993
22. Lackman RD et al. Intralesional curettage for grades II and III giant cell tumors of bone. Clin Orthop Relat Res 2005; 438:123-127.
23. Quint U, Muller RT, Muller G. Characteristics of phenol. Instillation in intralesional tumor excision of chondroblastoma, osteoclastoma and enchondroma. Arch Orthop Trauma Surg 1998;117:43-46.
24. Trieb K, Bitzan P, Lang S, Dominkus M, Kotz R. Recurrence of curetted and bone-grafted giant cell tumours with and without adjuvant phenol therapy. Eur J Surg Oncol 2001;27:200-202.
25. Capanna R, Sudanese A, Baldini N, Campanacci M. Phenol as an adjuvant in the control of local recurrence of benign neoplasms of bone treated by curettage. Ital J Orthop Traumatol 1985;11(3):381-8.
26. Di Caprio MR, Boyle J, Gibbs CP. Use of the Argon Beam Coagulator as an Adjuvant for treating bone tumors. Techn Orthop 2007;22(2):110-115.
27. Lewis VO et al. Argon beam coagulation as an adjuvant for local control of giant cell tumor. Clin Orthop Relat Res 2007;454:192-7.