

Local Adjuvants in Surgical Management of Bone Lesions

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Abstract

One of the most common methods for surgical treatment of bone metastasis is curettage. Local adjuvants are used to improve the effect of curettage in local cancer surgery and they may exerted their effects either chemically either physically; in orthopaedic oncology the most common are phenol, liquid nitrogen, laser, cement and argon beam coagulation. The purpose of this article is to review 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.

Keywords

Local Adjuvant, Bone Lesions, Orthopaedic Oncology, Cryotherapy

1. Introduction

At the beginning of the 1970s was described the first local adjuvant used in orthopaedic oncology surgery, liquid nitrogen cryotherapy, developed by Marcove at Memorial Sloan-Kettering Cancer Center of New York, and PMMA cementation, described for the first time by Persson and Wouters in 1976. Over time have been used other local adjuvants: these are both chemical, such as phenol, ethanol and hydrogen peroxide (H₂O₂), and physical, such as cement added with antiblásticos, and above all Argon beam coagulation, based on thermo-ablation and cryosurgery with cryoprobes.

The use of these substances is aimed at extending the results surgically obtained by curettage through the elimination of any remaining neoplastic cells. Margin status of the curettage is associated mostly with a risk of local recurrence. The application of a tumoricidal agent as a local adjuvant to the tumor bed has been shown to decrease local recurrence rates.

Local adjuvants play an important role in surgical treatment of metastatic lesions of the skeleton. Generally

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the surgeon's personal experience determines the choice of the adjuvant. In the last years their utilization has led to a significant reduction in the percentage of local recurrences.

It's important to remember that the surgical curettage remains the main treatment and any physical or chemical agent used as an adjuvant cannot correct a badly performed curettage. This is crucial to the oncological success of the surgical procedure. In fact, it must be done aggressively by using high-speed drill and by eliminating the residual material left by burr drilling. In this review we analyse chemical and physical aspects of the most common local adjuvant used in bone oncology.

2. Liquid Nitrogen

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

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. We need to consider what happens to a cell at such low temperatures, in order to emphasize the rationale of the method: the formation of ice crystals (which is due to rapid freezing and causes direct cell death), intracellular dehydration and toxic electrical imbalance, thermal shock, microvascular alterations and the disruption of the cell membrane (during a slow thaw and cause secondary and progressive cell death). A freeze-thaw cycle causes these crystals to coalesce and then mechanically disrupts the cell membrane, with consequent cell death. Cellular necrosis occurs at various temperatures between -21° and -60° , beyond this range the percentage of necrosis does not increase.

Different tissues do not respond to cryotherapy in the same way: their response depends on cell typology, tissue vascularization, density, presence of cryoprotective molecules, number of freeze-thaw cycles and the absolute temperature reached in the process and duration of procedure.

Golden rule in the procedure described by Marcove, from a technical point of view, is the following: a tourniquet, wide soft tissue retraction and protection and nerve vascular structure, aggressive motorized curettage, with high-speed drill, of the tumor with the creation of a large bone window. Then after curettage, liquid nitrogen is poured into the tumor cavity through a funnel sealed at the base with Gelfoam (Figure 1). To allow the Gelfoam to freeze and completely seal the system, the first pouring of liquid nitrogen lasts only 2 minutes; monitoring the temperature of soft tissues with thermocouples; it has been recognized that after the first cycle conductivity of the cold temperatures increases.

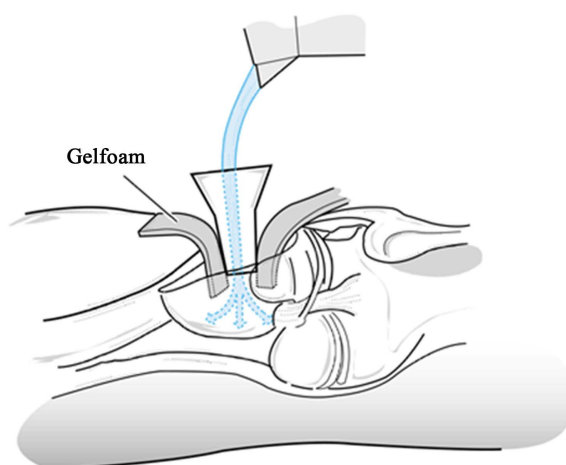


Figure 1. Liquid nitrogen technique in a GCT of the lateral femoral condyle. After the curettage of the tumor, liquid nitrogen is applied on the tumor bed through a stainless steel funnel, protecting the surrounding soft tissue with gelfoam layers (Chapman's Orthopaedic Surgery © 2001 Lippincott Williams & Wilkins).

Freeze-thaw cycles must last for 5 minutes; the tissue has to be frozen up to -40° , then thaw begins and once a temperature of 0° is reached another freeze-thaw cycle is administered (only one cycle should be administered if a physis is still open); irrigating the cavity with saline solution; reconstruction of soft tissues; intra-articular monitoring with thermocouples. Next step is reconstruction with PMMA and internal fixation to provide immediate stability, structural support and allow early rehabilitation of the adjacent joint (for 6 weeks weight-bearing is not allowed); postoperative prophylactic antibiotics. The cytotoxic efficacy of cryosurgery has no effect on articular cartilage with a range of 7 - 12 mm. The effect on bone structure is trabecular necrosis with the interruption of osteoid matrix and extensive bone marrow necrosis with minimal inflammation, and subsequent liquefaction with progressive fibrosis. One of the most common complications related to this technique is rate of 5% - 25% of fractures of the part treated with cryosurgery. Cryonecrotized bone tissue behaves as an acellular graft and the ossification is very slow [7] [8].

An evolution within the field of cryosurgery are cryoprobes. There is a different application of low temperatures through local conduction and not through instillation, there is no need to isolate the funnel; are used Argon at -190° as freezing agent and Helium at 35° as thawing agent. Some systems use only Argon, by regulating gas pressure its temperature can be determined using the Joule-Thompson effect with the aid of computerized systems. In this way there is a more effective control of the temperature achieved and a faster freezing temperature compared to the system using liquid nitrogen (**Figure 2**).

Physiological solution is utilized both as a thermal conductor, to conduct the cold into the lesion only up to its rim and to avoid contact with adjacent tissues, and as thermo-modelling agent by making any frozen residual part of the physiological solution itself melt to irrigate and protect the adjacent tissues. In alternative to physiological solution, Surgilube, a viscous jelly utilized in urology and gynaecology can be used [9]. The steps following cryoprobe technique are identical to those of traditional cryosurgery [10]. Cryoprobes are used to treat smaller lesions because, however, has its limits in the number, diameter and cost of each cryoprobe, volume of pressurized Argon, the time needed to administer repetitive freeze-thaw cycle. Liquid nitrogen following Marcove's technique remains the gold standard to treat more rapidly and more cheaply major bone cavities.

3. Acrylic Cement PMMA

Charnley had demonstrated that an acrylic cement (polymethyl-methacrylate) mass of the size of a golf ball could reach with an exothermic reaction the temperature of 90°C [11]; then in 1976 Persson and Wouters introduced into the treatment of bone lesions the use of PMMA-based cement [12]. To destroy gonadal, embryonic, blood cartilaginous and neoplastic cells is sufficient a temperature between 42°C and 47°C . The advantage of this method lies in preserving the skeletal segment, rapid recovery of weight-bearing ability, local control, easy recognizing of a local recurrence with the possibility of other therapies [13].

It was assumed that PMMA induces perilesional tissue necrosis in two ways: by means of the heat produced by the cement exothermic polymerization and a possible toxic effect of the monomer itself.

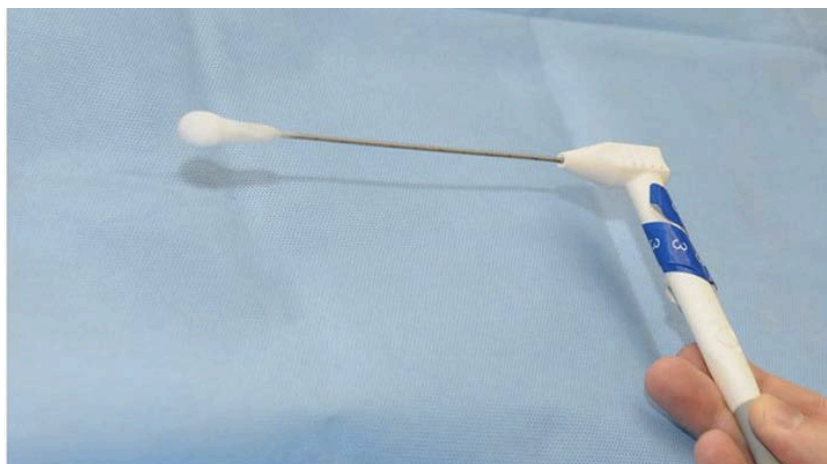


Figure 2. Percutaneous cryoprobe creating an ice ball. Probe manufacture by Cryo-care Endocare CS, Irvine, CA, USA.

In many experimental studies, however, have been demonstrated that the thermal necrosis of the bone is induced within a temperature range of 48°C - 60°C and it is time-dependent, while in an experimental study the maximum temperature of the bone/cement interface reached was 46°C. As it is mass and form dependent [14], the latter was reached in a condition, in which the temperature of the nucleus of the mass cement increases proportionally depending on the size of the mass itself. Furthermore, the effect is greater if the blood flow is interrupted by a tourniquet application because the speed of heat dissipation depends on the bone vascularization.

In different experimental studies an evident cellular toxic effect of the methyl methacrylate monomer wasn't found [15]. The range efficacy of the cement is between 1.5 - 2 mm of the spongy bone and 0.5 mm of the cortical bone [16].

Cement is utilized not only as filler but also as material to reinforce an intramedullary fixation, such as a locked nail. In these cases perform reaming at least 2 mm beyond the largest nail calibre possible and try reducing the fracture before the introduction of cement. The cement must be low-viscosity cement and has to be cooled to slow down the speed of polymerization and then, in case of permeating bone lesions, introduced into the whole diaphysis. After the cementation of the canal the intramedullary nail is locked in static mode. Instead, in localized lesions osteosynthesis device has to be fixed on cement, which has to fill the space left by curettage [17].

4. Cement Riched with Antibiotics and Antiblastics

Antibiotic-loaded acrylic cement (Table 1) can be useful for locally administering a high drug dose, which cannot be done through systemic administration without general complications and toxicities (Table 2) [18].

In this method, also anticancer drugs are mixed with acrylic cement PMMA to use a slow release effect from within the cement. The most commonly used drugs are methotrexate, aspecific, cisplatin for lung tumors and doxorubicin for breast cancer [19]. Rosa (Figure 3) [20] demonstrated that with this technique anticancer drugs tend to form granules and are activated from the cement with the passage of time.

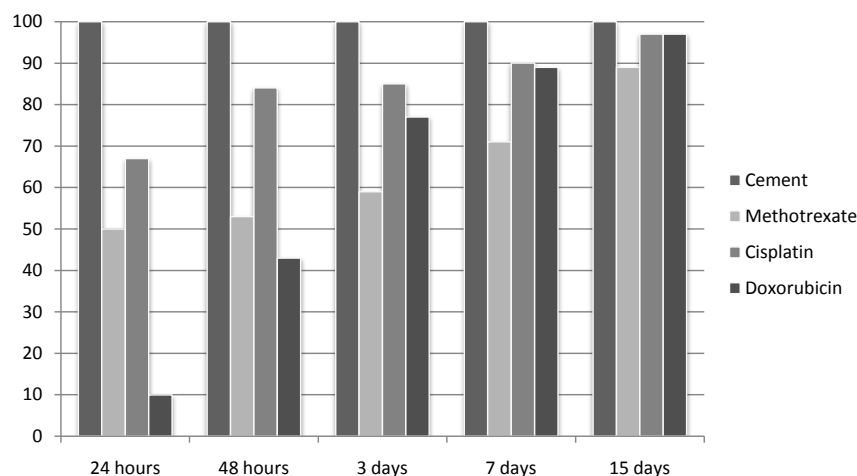


Figure 3. Histogram showing the results of the MTT (3-[4,5-dimethylthiazol-2-y1]-2,5-diphenyl-tetrazolium bromide; Sigma) test from the second set of experiments. Cell survival with the three antineoplastic drugs is shown at 24 and 48 hours and 3, 7 and 15 days.

Table 1. Commercially available antibiotic PMMA products.

Product	Distributor	Viscosity	Antibiotic
Cemex Genta	Exatech	Low	Gentamicin (1.0 g)
Cobalt G-HV	Biomet	High	Gentamicin (0.5 g)
Palacos R + G	Zimmer	High	Gentamicin (0.5 g)
Simplex P	Stryker	Medium	Tobramycin (1.0 g)
Smartset GHV	DePuy	High	Gentamicin (1.0 g)
Smartset GMV	DePuy	Medium	Gentamicin (1.0 g)
Versabond AB	Smith Nephew	Medium	Gentamicin (1.0 g)

Table 2. Antibiotics mixed with PMMA copolymer powder used in pharmacological testing and elution rates from ALAC cylinders.

Antibiotic	Formulation	Dose per 40 g of PMMA powder	API per 40 g of PMMA powder, g	API per sample of ALAC resin, g	API per 400 mg ALAC cylinder, µg
Amikacin Sulfate (CT Laboratories, Sanremo, Italy)	Liquid	4 mL	1	0.73	5344
Gentamicin Sulfate (Fujan Fukang Pharmaceutical Co., Fuzhou, China)	Powder	4 g	2.4	1.76	12,884
Streptomycin Sulfate (Laboratorios Normon SA, Madrid, Spain)	Powder	4 g	3	2.2	16,105
Tobramycin Sulfate (IbiGiovanni Lorenzini SpA, Aprilia, Italy)	Powder	4 g	2.8	2.05	15,007
Teicoplanin (Sanofi Aventis, Paris, France)	Powder	4 g	3.3	2.42	17,716
Vancomycin Hydrochloride (Xellia Pharmaceuticals AS, Oslo, Norway)	Powder	4 g	4	2.93	21,450
Lyophilized	Powder	4 g	4	2.93	21,450
Ceftriaxone Sodium (Fidia Pharmaceutical SpA Abano Terme, Italy)	Powder	4 g	3.3	2.42	17,716
Clindamycin Phosphate (Pfizer Inc., New York, New York)	Powder	4 g	3.5	2.56	18,741
Colistin Sulfate (UCB SA, Brussels, Belgium)	Powder	3,000,000 IU	0.24	0.18	1318
0.6%					
2.4%	Powder	12,000,000 IU	0.96	0.7	5124
Meropenem (Astra Zeneca, London, United Kingdom)	Powder	4 g	3	2.2	16,106
Rifampicin (Sanofi Aventis)	Powder	4 g	4	2.93	21,450
Tigecycline (Pfizer Inc.)	Powder	1.5 g	0.5	0.37	2709

Abbreviations: ALAC, antibiotic loaded acrylic cement; API, active pharmacological ingredient; PMMA: polymethylmethacrylate.

Each drug conserves its own cytotoxic characteristics with a different effect on the cell vitality of the related culture. It is important that the heat induced by polymerization does not affect the pharmacodynamic features of these drugs, neither modified mechanical properties in term of compressive tests [21].

Even if the studies on cell cultures have 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.

5. Argon Beam Coagulation

Electric current has been advocated as adjuvant treatment after curettage of aggressive and benign bone tumors. 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. 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.

Argon beam photocoagulation has gained popularity as a local adjuvant in the treatment of benign or aggressive bone tumors. In this technique, developed within the field of laparoscopy, an argon beam is used to conduct electric current to the tissue.

Histological aspect with argon coagulation results in tissue vaporization, carbonization and coagulative necrosis, dependent on width, power and time. 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 [22] [23]. Different depth of action depends by the power assigned, in fact as demonstrated in Heck *et al.*

study from 50 W to 150 W, after histologic evaluation the necrosis' depth is between 0.1 ± 0.1 mm to 4.2 ± 0.7 mm [24]. Tissue desiccation causes tissue carbonization, thus the cavity tends to assume a characteristic dark colouring. As data in medical literature confirm, this technique is easier to manage than others [25]; In fact argon beam coagulation has been considered a safe and reasonable adjuvant treatment with low recurrence rates.

6. Phenol

Phenolic acid, also called phenol, has different activity in relation with its concentration: is a bacteriostatic compound in a concentration of 0.1% - 1%, bactericide above 1%, cytotoxic, non selective in concentrations higher than 3% and local anaesthetics in concentration higher than 5% [26]. Phenol acts through denaturation of cellular proteins which determine cell permeability leading to actual destruction of the cells. It also can destroy about 1 - 1.5 mm of tumor tissue through coagulative necrosis, it also can be used in association with PMMA.

Phenol is produced physiologically by human intestine and normal concentration of phenol in the human body is about 0.1 mg/l. Phenol derive by the natural destruction of aromatic amino acids in the intestine and is normally excreted via the kidney through urine metabolites, maximum urine concentration allowed in a working environment is of 300 mg/l urine. It exerts bad effects on the function of the heart, lungs, kidneys and the nervous system. In a concentration of 5% at ambient temperature, phenol is selectively indicated for cartilage tumors, and either is directly poured into the tumor cavity or applied to the cavity surface with a tampon.

Before phenol instillation it is important to wash the cavity in order to remove any tissue debris or clots, being extremely careful not to damage or irrigate the periskeletal soft tissue. This procedure has to be repeated three times, in order to cover the inner wall of the cavity homogeneously irrigating wall clots and avoiding marginal dilution of arrival blood. After the instillation the amount of phenol needed has to be left in situ for 1 minute, then it has to be removed through a physiological solution wash. In other studies, however, phenol concentrations of 90% which is left in situ for 5 minutes and then washed with physiological solution [27]. After this washing, physiological solution has replaced both the 70% ethanol irrigation, because phenol is easily soluble in water in concentrations of 5% and it is highly toxic, and eventually the irrigation with hydrogen carbonate solution [28].

In a study by Trieb *et al.* [29] 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.* [30] describe a recurrence rate of 7% in cancers treated with phenol compared to the 41% of those ones treated without phenol out of 165 different benign tumours with a recurrence potential.

7. Ethanol

Ethanol causes tumoral tissues necrosis by denaturing cellular proteins, degenerating cellular cytoplasm, and exerting a thromboembolic effect on the small vessels supplying the tumor [31]. Ethanol in high concentration is less toxic and easier available than some other chemical adjuvant. Its toxicity doesn't extend deeply into surrounding bone and its adverse effects are minimal on the adjacent tissues.

Ethanol is readily available in most surgical suites and has been used as adjunctive treatment for various soft tissue tumors, such as hepatocarcinoma [32] [33], thyroid lesions [34], pheochromocytoma [35]; and in skeletal localization such as osteoid osteoma [36], hemangioma [37] [38], and skeletal metastases [39] [40]. Ethanol also was used in the treatment of GCTs in two case series [41] [42], neither of which found ethanol-related complications; the recurrence rate after use of ethanol isn't widely different from the use of other adjuvants for GCT of the bone.

8. Hydrogen Peroxide

Hydrogen peroxide (H_2O_2) is usually used three-percent nondiluted as local adjuvant, and is also hypothesized to reduce surgical site infection risk. Some retrospective review has shown it's important as a local adjuvant in the surgical treatment of giant cell tumor; there aren't studies that report hydrogen peroxide efficacy in the treatment of soft tissue sarcomas [43]. Using H_2O_2 is recommended because is low cost and low risk adjuvant even if there aren't studies that demonstrated statistical result as local adjuvant [44].

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