Incidence of Intracorporeal Complications of Cryotherapy in Bone Tumors Surgery

A Systematic review and meta-analysis for partial fulfillment for the master degree in Orthopaedic Surgery.

By

Ali Ahmed Ali

M.B.B.Ch

Faculty of Medicine -Ain Shams University

Under Supervision of

Prof.Dr.Mohamed Abdel Rahman Mostafa

Professor of Orthopaedic Surgery
Faculty of Medicine-Ain Shams University

Dr.sherif Ishak Azmy

Lecturer of Orthopaedic Surgery
Faculty of Medicine-Ain Shams University

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Ali Ahmed Ali

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List of abbreviations

ABC	Aneurysmal bone cyst.
CL	Confidence limit.
DHS	Dynamic hip screw.
FEM	Fixed effects method.
GCT	Giant cell tumor.
NOF	Non ossifying fibroma.
OA	Osteoarthritis.
PMMA	Polymethylmethacrylate.
RCT	Randomized controlled trials.
REM	Random effects method.
TKA	Total knee arthroplasty.

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Abstract

The cryotheryapy agents such as liquid nitrogen have been used as adjuvants to the surgical techniques in the treatment of variety of benign aggressive bone tumors. Early studies showed high rates of complications from usage of these agents that included local recurrence, fractures, skin necrosis, infections, neurapraxia and growth plate damage. The objective of our review is to determine the incidence of these complications.

Ten studies are identified for analysis from 1968 to 2017 that included 328 patients who were treated with lesion excision and extended curettage and pouring of liquid nitrogen into the curettaged bone cavity.

The review detected rates of complications that followed pouring of liquid nitrogen into the bone cavity of these patients. With modified techniques and usage of internal fixation, bone grafts and cementation, these rates became less than showed in the earlier studies.

The cryotherapy is a flexible tool to be used as an adjuvant to the excision of benign aggressive bone tumors with extended curettage.

Keywords:

Cryotherapy.
Liquid nitrogen.
Bone tumors.
Benign aggressive bone tumors.
Complications.

Introduction

The cryotherapy was initially used in the 17th century by the Greeks. In 1850, it was applied for dermatological purposes, the anesthetic and the vasoconstrictive effects. James Arnott[1] was the first to use cryotherapy in treatment of skin lesions, breast cancer and cervical cancer.

Marcove and Miller[2] were the pioneers to use the cryotherapy in the orthopedic surgery and showed that liquid nitrogen seems to have a good local control of tumors with minimal postoperative defects in bone stock and joint function.

Marcove[2] first reported the use of cryotherapy in 1969 in treatment of metastatic carcinoma of the humerus. Later on, he described the direct pouring method of liquid nitrogen to fulfill the tumor cavity many times. The method was consisted of the wide incision, thorough curettage and repeated exposure of the bone cavity to temperature below -20^{o}c by liquid nitrogen. This method was described as physical adjuvant aiming to decrease the higher rate of local recurrences after the curettage only thereby decreasing the need for extensive resection and reconstruction process by prosthesis, the arthrodesis and allografts. Subsequently, cryotherapy was applied in the treatment of many benign and metastatic bone tumors as well as primary bone sarcomas.

Marcove[2] has concluded that the cryotherapy should be reserved for the benign aggressive bone tumors. He showed that surgical treatment of high grades of bone sarcomas usually requires wide excision of the soft tissue components; so any violation of these tumors margins would be associated with high incidence of local recurrence.

The cryotherapy is not an appropriate modality for high grades primary bone sarcomas as it is used through intralesional surgical procedures while the surrounding the soft tissue component of the high grade tumors is protected from the freezing effects of the liquid nitrogen throughout the procedure. The metastatic and benign lesions are usually confined to the bone and rarely have marked soft tissue components, so an adequate intralesional procedure can achieve local control for a long time making cryotherapy suitable for this purpose.

However, initial studies by Marcove described high complications rate up to 51% which included fractures, skin necrosis, infection and nerve lesions[3]. These high rates of complications have led to refinement of the surgical procedures such as aggressive burring and experience with the techniques helped to reduce these rates with time[4].

Cryobiology

It is the study of the physical effects of changes in temperatures on the living tissues. Freezing of tissues is quietly complicated process because the water is divided into intracellular and extracellular compartments by the cell membrane[5].

Tissue necrosis occurs through two mechanisms; immediate and delayed cell destruction.

Immediate cell death:

The cell membrane is permeable for water, but less permeable for the solutes. When tissues cool slowly, they first enter super cooling phase without ice formation.10^0c to 15^0c temperatures initiate the ice formation in the extracellular compartments, while the intracellular compartments[6] remain unfrozen because of presence of high and low molecular weight substances. Freezing of the extracellular compartment water causes the concentration of solutes to rise and subsequently drives water from the intracellular to the extracellular compartment as a result of the osmotic pressure. This water loss makes the cell to shrink and accompanied by high concentration of solutes, which further inhibits ice formation in the intracellular compartment and causes cell injury[7]. This is an important process during slow cooling.

The very rapid cooling enhances ice formation in the intracellular compartment as there is too little time for

water to across the membrane to outside to maintain the osmotic equilibrium on both sides[8].

The frozen tissues are proposed to shearing forces and ice extension that induces mechanical damage to the cell membrane and dysfunction of the cell organelles[9]. The slow thawing is associated with recrystallization of intracellular ice crystals so that their damaging effect can be exploited a second time [8]. The slower the thawing, the larger ice crystals will grow and the more mechanical damage to the cell.

Delayed cell destruction:

After thawing, there is usually a brief period of the vasodilatation. Furthermore, the vascular endothelium is sensitive to the freezing and the thawing processes and increases the permeability of vascular walls, interstitial edema, slow circulation and platelets aggregation [10].

Ischemia in the tissues treated by the cryotherapy deprives all cells of any possibility to survive and causes uniform necrosis of these tissues except at the periphery of lesions. In bone lesions, microangiopathy has showed total avascularity of the cortex after the cryotherapy application[11].

The studies [12] showed that destruction of a long term frozen tissues is more intense while holding the freeze than when the freeze is not held. Repetitive cycles of freeze-thaw are recommended as the living tissues become more resistant to thermal damage, after first cycle, conductivity

of thermal effect is increased, and the specific heat capacity and the vascularity of tissues are decreased. So, these effects prepare the tissues to make the next cycle more effective by the faster cooling and slower thawing.

The histological changes of the bone treated by cryotherapy are seen after several days. The osteocytes disappear slowly, within 7 days there are no living cells. Few days later, osteogenesis appears at the periphery of devitalized bone segment and replaces the dead bone. During this period the bone is weak and fractures easily occur[13].

Indications

It is indicated for a variety of benign aggressive and low grade malignant lesions. These lesions tend to occur in the metaphysis and epiphysis of long bones, marginal or wide excision would cause segmental loss and compromise the growth plates in children and damage the articular cartilage. Also, excision at these sites requires major reconstruction with prosthesis and segmental grafts while the technique of the intralesional excision and curettage combined with the local adjuvant cryotherapy is indicated for these types of tumors. After curettage, the minor reconstruction will be sufficient[14, 15] .

Histologic diagnosis

*Benign –aggressive bone tumors

- Giant cell tumor.
- Simple bone cyst.
- Aneurysmal bone cyst.
- Fibrous dysplasia.
- Enchondroma.
- Chondroblastoma.
- Osteoblastoma.
- Eosinophilic granuloma.
- Chondromyxoid fibroma.

*Low grade sarcomas of bone

-Low grade chondrosarcoma.

*Metastatic bone tumors