Surgical treatment of giant cell tumour of long bone with anhydrous alcohol adjuvant

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Abstract This study was designed to evaluate the feasibility and effectiveness of the use of anhydrous alcohol as an adjuvant treatment for giant cell tumours (GCTs) of long bone. Between October 1989 and January 2004, 42 GCT patients were treated and followed up for an average of 4.1 years (range 1–13 years). Mean patient age was 34 years (range 17–67 years). After curettage and additional burring, anhydrous alcohol was used as an adjuvant therapy in all patients before the bone defect was filled with bone graft or cement. Four patients (9.5%) experienced local recurrence. There were no alcohol-related complications. Recurrence-free probability was 87.6% at final follow-up (13 years) after index surgery by Kaplan–Meyer analysis. Our data suggest that anhydrous alcohol can be used as an effective safe adjuvant for the treatment of GCT of long bone.

Résumé Cette étude a été réalisée dans le but de prouver l'éventuelle efficacité de l'alcool anhydre dans le traitement auxiliaire des tumeurs géantes de l'os long (également appelées GCT : Giant Cell Tumors). Entre octobre 1989 et janvier 2004, 42 patients atteints de GCT ont reçu un traitement à base d'alcool anhydre sur une durée moyenne de 4,1 ans (durée comprise entre 1 et 13 ans selon les patients). L'âge moyen de ces patients était de 34 ans (entre 17 et 67 ans). Après curettage et ébarbage additionnel, l'alcool anhydre est employé comme thérapie adjuvante sur l'ensemble des patients avant d'appliquer le ciment sur l'os ou de transplanter le greffon. Il n'a pas été fait état de complication causée par l'application de cet alcool. 4 patients ont rencontrés des problèmes de rechute. En revanche dans 87,6% il n'a pas été fait état de rechute. Nos données suggèrent que l'alcool anhydre peut être employé comme un adjuvant efficace pour le traitement des GCT de l'os long.

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Introduction

Giant cell tumour (GCT) is one of the common primary bone tumours and has been also referred to as osteoclastoma because it is composed of many multinucleated osteoclast-like giant cells. According to the Mayo Clinic series, GCT represents 5% of bone neoplasms and typically occurs in patients between the ages of 20 and 40 years, with a slight predominance in women. Roentgenographic findings show an eccentrically osteolytic and destructive bony lesion in the epi-metaphysis of a long bone. Cooper and Travers first described GCT in 1918, and Nelaton noted its local aggressiveness. Despite its histologically benign features, the prevalence of pulmonary metastases in GCT has been estimated to be approximately 2% to 3% [1, 4],

and primary and secondary malignant GCTs have been reported [20, 22].

Historically, the treatment consisted of simple curettage, but the subsequent recurrence rate after simple curettage was high (about 30% to 50%) [24]. The generally accepted treatment for GCT of long bone is thorough intralesional curettage and reconstruction by bone graft or polymethyl methacrylate cement filling, or both. Limb salvage procedures by allograft or tumour prosthesis may be performed for widely resected tumours. Moreover, recent reports indicate that aggressive curettage, often combined with adjuvant treatment, results in local recurrence rates of less than 10% [2, 6, 9, 12, 13, 15, 19, 25]. The currently used adjuvants to kill tumour cells remaining after intralesional curettage include hydrogen peroxide (H_2O_2), phenol, liquid nitrogen, distilled water, and electrocautery.

This study was designed to evaluate the feasibility and effectiveness of the use of anhydrous alcohol (99.8%, ethyl alcohol, CH_3CH_2OH) as an adjuvant in the treatment of GCT of long bone and to describe its complication rate. We analysed the overall recurrence rates of those treated with anhydrous alcohol, and Kaplan–Meier curves were used to determine recurrence-free probability and time to recurrence.

Patients and methods

One hundred and three patients diagnosed as having GCT of long bone were treated and followed up at a single institution from October 1989 to January 2004. Wide resection with or without skeletal reconstruction was performed in 30 patients with soft tissue invasion, joint involvement, pathological fracture, or multiple recurrences. Curettage, additional burring, and reconstruction by bone graft or cementing with or without internal fixation were performed in 73 patients. Our criteria for these treatment protocols were: (1) giant cell tumour of long bone (2) with a cavitary lesion and (3) without a concomitant pathological fracture. No additional adjuvant treatment was given to 31 of these patients. The other 42 patients who had been treated with anhydrous alcohol as an adjuvant after intralesional resection were studied retrospectively and constituted the study population.

Patients were followed up for an average of 4.1 years (range 1–13 years). There were 13 (31%) men and 29 (69%) women of mean age 34 years (range 17–67 years). The most common location was the distal femur (17 patients), followed by the proximal tibia (12 patients). Thirty four of these patients (81%) were newly diagnosed with GCT at our institution, and eight patients were referred to us after operation at other institutions.

According to the Enneking staging system, one lesion was stage 1, 38 lesions stage 2, and three lesions stage 3.

After extensive intralesional curettage of the tumour through a cortical window, a motorised burr was used to remove an additional few millimeters of cancellous bone. The curetted cavity was then irrigated with saline solution using pulsatile lavage. After the cavity had been dried, it was filled with anhydrous alcohol for 30 s to 60 s and washed out. The lesion was kept level with the ground to prevent overflow, and the surrounding normal soft tissue was carefully protected from the alcohol. This process was repeated for a total alcohol contact time of 5 to 10 min. After copious irrigation with normal saline solution, autogenous iliac or allogeneous bone graft, or polymethyl methacrylate (PMMA) cement, was used to fill the bone defects. Early in this series, we usually reconstructed cavities by bone grafting, but currently we prefer a PMMA cement filling because polymethyl methacrylate allows immediate weight bearing and, theoretically, provides additional tumour “kill” as it sets. If most of the stress-bearing articular surface area was undermined by curettage, we placed a thin layer of autogenous bone graft between the exposed subchondral bone and the underlying cement to provide a stress-absorbing layer between the pliable articular surface and the polymethyl methacrylate cement.

Results

Four (9.5%) patients who received anhydrous alcohol treatment developed local recurrence, *whereas 15 (48.4%) developed recurrence out of 31 patients who had not received any adjuvant treatment*. The mean interval between the index operation and recurrence was 20.2 months (range 4–37.2 months). *Cementing was the initial method of defect filling in three patients with recurrence, and autogenous bone grafting and cementing was used simultaneously in one patient*. By Kaplan–Meyer analysis, recurrence-free probabilities were 87.6% in the final follow-up (13 years) after the index surgery (Fig. 1). One of the patients with recurrence had a malignant transformation at 26.4 months postoperatively. In this case, after the index operations, the diagnosis of a giant cell tumour was confirmed by experienced bone pathologists, but the specimen obtained at the second operation was diagnosed as osteosarcoma of the giant cell-rich type. This patient also developed a pulmonary metastasis, which was confirmed by biopsy. Finally, he was treated by wide resection and reconstruction with a tumour prosthesis, pulmonary resection of the metastasis, and adjuvant chemotherapy. These four patients are currently disease free (Table 1).

Five (11.9%) complications developed. Three patients complained of knee pain on weight bearing. In these

Fig. 1 Kaplan-Meier analysis and log-rank testing revealed that the use of anhydrous alcohol adjuvant significantly ($P=0.014$) reduced the recurrence rate of giant cell tumours of long bone

patients, bone cement was used for bone defect reconstruction and mild osteoarthritis was evident on plain radiographs. One patient had partial ankylosis of the knee joint. The last patient had a wound problem, which was treated by thorough debridement in the operation room. However, the culture report showed negative results, and a biopsy revealed a cement-related foreign body reaction (Table 2). There were no anhydrous alcohol-related complications.

No statistical difference was found between recurrence and age, gender, tumour stage, or anatomical location.

Discussion

Because a high local recurrence rate is the main issue in the treatment of GCT of long bones, many surgeons have tried to reduce the recurrence rate with preservation of joint function. Early treatment methods of GCT involved simple curettage with or without a bone graft, and the consequent recurrence rate was approximately 40%. In 1969 Vidal et al. [26] introduced reconstruction with bone cement after

thorough intralesional curettage, and many authors have reported reduced local recurrence rates using this method [2, 5, 17, 19, 21, 26]. Subsequently, O'Donnell et al. [19] reported a local recurrence rate of 25% in a large population after a prolonged period of follow up. Most reports published since have documented recurrence rates between 0% and 29%.

Blackley et al. [3] reported a 12% local recurrence rate in a study of 59 GCT patients who were treated by curettage using a high-speed burr and autogenous bone graft reconstruction with or without allograft bone. They noted that the adequacy of tumour removal, rather than the use of adjuvant modalities, is what determined the risk of recurrence. However, the reduction of local recurrence by adjuvants is generally accepted by many surgeons. After intralesional curettage of GCT of long bone, several adjuvant treatment methods, i.e., additional burring, phenol, H_2O_2 , cryotherapy using liquid nitrogen, and electrocautery have been advocated, including conventional radiation therapy, which is no longer used in long bone because of the potential risk of malignant transformation. Kirchen et al. [11]

Table 1 Data of patients with recurrence (*F* female, *F* male, *CRT* curettage, *IBG* iliac bone graft, *CMT* cement, *WR* wide resection)

Gender/ age (years)	Site	Stage ^a	Recurrence (months)	Initial treatment	Treatment after recurrence	Follow up period (years)	Comments
F/22	Distal femur	2	37.2	CRT, IBG, CMT & alcohol	CRT, IBG & alcohol	3.1	
M/22	Distal femur	2	13.2	CRT, CMT & alcohol	CRT, CMT & alcohol	4.5	
M/24	Distal femur	2	26.4	CRT, CMT & alcohol	WR & prosthesis	6.2	Malignant transformation to osteosarcoma with lung metastasis
F/19	Fibular head	2	4.0	CRT, CMT & alcohol	En bloc resection	2.2	

^a Enneking stage

Table 2 Complications in the patients (*F* female, *CRT* curettage, *IBG* iliac bone graft, *CMT* cement)

Gender/age(years)	Site	Stage ^a	Complication	Treatment	Follow up (years)	Comments
F/34	Distal femur	2	Osteoarthritis	CMT removal & IBG	8.3	Culture (–)
F/21	Proximal femur	2	Wound discharge	CRT & CMT	3.4	
F/24	Proximal tibia	2	Osteoarthritis	CMT removal & IBG	8.9	
F/32	Distal femur	2	Partial ankylosis	Arthroplasty	6.2	
F/30	Proximal tibia	2	Osteoarthritis	CMT removal & IBG	7.0	

^a Enneking stage

reported that methotrexate eluting from bone cement provides locally effective chemotherapy without the risk of systemic toxicity. Published reports document reduced recurrence rates of 9.1 % for phenol [6] and 7.9 % for liquid nitrogen [13]. However, phenol is a well-known pollutant and is a potential carcinogen. Phenol can be fatal if inspired and may cause nerve damage and burns to the skin, mucosa or eye. Protective devices are necessary to handle it, and electrocautery must be avoided during phenol application to avoid the risk of fire or explosion. On the other hand, Trieb et al. [25] reported no significant reduction in the local recurrence rate after using phenol as an adjuvant. Cryosurgery using liquid nitrogen also presents the risk of considerable complications, such as fracture, adjacent tissue necrosis, failure of grafted bone to incorporate, and nerve injury [5]. In addition, the depth of the necrotic margin is difficult to control when liquid nitrogen is used. Radiation therapy, first described by Ewing, is associated with a high rate of secondary malignancies and is no longer applicable in routine cases [14]. PMMA bone cements are also accepted adjuvants because of the local effects of hyperthermia during polymerization and of the cytotoxicity of the unpolymerised monomer [17–19, 21, 24]. In this study, cavities were reconstructed by bone grafting or cementing.

In the histology field, anhydrous alcohol is used as a fixative, because it arrests autolysis and bacterial decomposition and preserves cells and tissue constituents in a near life-like state. Alterations of protein structure by ethyl alcohol are primarily due to the disruption of hydrophobic bonds that contribute to the tertiary structure. In addition, anhydrous alcohol can distort nuclear details and shrink cytoplasm. If fixation is prolonged, alcohol removes histones from nuclei and later extracts RNA and DNA, which is also significant in the context of tumour necrosis [16]. Fujimoto [7] reported that ethyl alcohol injected into normal liver tissues, liver cirrhosis nodules, or hepatocellular carcinoma nodules in denatured rat hepatocytes causes coagulative necrosis. Shiina et al. [23] reported that ethyl alcohol causes tumour necrosis by degenerating cellular cytoplasm and completely denaturing cellular proteins with irreversible vascular thrombosis of small vessels supplying the tumour. In addition, successful results have been

reported for percutaneous injection of ethanol into hepatocellular carcinoma. Ethyl alcohol has also been used to treat thyroid cysts, hyperparathyroidism, benign prostate hypertrophy, and pheochromocytoma of the adrenal gland [8, 10, 27].

From these experiences in other fields, we decided to examine the effect of anhydrous alcohol in GCT of long bone. In this study we noted a significant reduction in the local recurrence rate among those who were treated with anhydrous alcohol, and we observed no alcohol-related complications. Gitelis et al. [9] and McDonald et al. [15] also introduced alcohol in their series, but they used it to rinse out phenol rather than to kill remaining tumour cells, because phenol is highly soluble in alcohol. Thus, to our knowledge, this study is the first report on the value of anhydrous alcohol as an adjuvant aimed at eradicating giant cell tumours of long bones. The recurrence rate of 9.5% found in the present study is comparable to other recently published series.

Clinically, adjuvant treatment of GCT with anhydrous alcohol achieved favourable results, but basic research in this area is lacking. For example, to arrive at a standard protocol one should optimise the alcohol concentration. A 70% alcohol solution is commonly used as a skin disinfectant. At this concentration, alcohol is easily able to penetrate bacterial cell walls and denature the proteins and enzymes inside the cell. A 95% alcohol solution may coagulate protein on the outside of the cell wall, which might make it difficult for the alcohol to enter the cell. In addition, the duration of alcohol treatment should also be standardised.

Although the results of our study were those of one senior author, the patients were not randomised and the alcohol treatment was performed comparatively recently. Thus, the surgeon's learning curve to curette the lesion might have affected the results. However, we firmly believe that the surgeon's learning curve had little effect on the outcome, because he was already familiar with this field of surgery.

In summary, based on the follow-up results of the patients with GCT of long bone treated with anhydrous alcohol as an adjuvant, it seemed that local recurrence was significantly reduced among those that received alcohol treatment. Our data suggest that anhydrous alcohol could be

used as an effective adjuvant without the potential risks of other adjuvant methods for the treatment of GCT of long bone. Long-term, randomised, prospective, clinical studies and more basic research should be undertaken.

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