April 30, 2002

Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Boulevard
Rockville, Maryland 20850

Re: Reclassification 21 CFR 888.3027
Polymethylmethacrylate (PMMA) Bone Cement
Filed: January 21, 1998

Dear Mr. Melkerson:

Enclosed please find in triplicate an amendment to the Reclassification Petition for Polymethylmethacrylate (PMMA) Bone Cement intended for pathological fracture applications. This amendment makes reference to the information that remains the same as previously submitted in the January 21, 1998 petition and includes the additional information as it pertains specifically to pathological fractures.

The pathological fractures reclassification amendment is being submitted under 21 CFR, Section 520 (l) to reclassify a transitional device from Class III to Class II based upon the information provided for the above referenced indication.

Your prompt attention to the submission is greatly appreciated.

Sincerely,

Thomas L. Craig

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Amendment to the Reclassification Petition for Polymethylmethacrylate (PMMA) Bone Cement (21 CFR 888.3027)

April 30, 2002

TABLE OF CONTENTS

SECTION I: REGULATORY HISTORY OF BONE CEMENT

The regulatory history of PMMA Bone Cement was presented in the January 21, 1998 Reclassification Petition. The following regulatory activity has taken place since that original petition submission.

The Petition for Reclassification of 888.3027 Polymethylmethacrylate (PMMA) Bone Cement was submitted to the FDA on January 21, 1998. The petition initially included all orthopedic applications with the intent to cover pathological fractures. However, the pathological fractures indication was unintentionally omitted from this petition.

Two addenda were submitted to the original petition. The first addendum was submitted on March 18, 1998 which included material changes in Sections V and VI, added four scientific articles to Appendix J, and made additions to the Clinical Results and Risks to Health sections further discussing Bone Cement Implantation Syndrome (BCIS). The second addendum dated March 27, 1998 presented responses for additional information requested by the FDA.

On April 28, 1998, the Orthopedic and Rehabilitation Advisory Committee (Panel) held a meeting to review the petition. The indications that were considered for reclassification were total joint arthroplasty applications. The Panel's recommendation was to reclassify (PMMA) bone cement from Class III to Class II. It was also during this Panel discussion that the members also mentioned pathological fracture indications for inclusion in the reclassification to Class II.

An October 14, 1999 letter from the FDA to OSMA effectively reclassified bone cement from Class III to Class II for use in arthroplastic procedures of the hip, knee, and other joints for the fixation of polymer or metallic prosthetic implants to living bone.

The Class II Special Controls Guidance Document: Polymethylmethacrylate (PMMA) Bone Cement 510(k)s; Final Guidance for Industry was issued by the FDA on August 2, 2001.

SECTION II: DEVICE DESCRIPTION

General Description

As indicated in the original January 21,1998 reclassification petition, PMMA bone cement is a self-curing, two component luting or grouting agent used primarily for the fixation of prostheses to living bone. Additionally, it is used for the fixation of pathological fractures with or without metallic fixation. The two components are a liquid component comprised of methyl methacrylate monomer, an accelerator, and a stabilizer and the powder component consisting of one or two polymers, a radiopacifier, and an initiator. When the powder and liquid components are mixed, polymerization occurs resulting in a hard bone cement in approximately 5 to 15 minutes.

Indications

Polymethlymethacrylate (PMMA) bone cement is indicated for the fixation of prostheses to living bone in orthopaedic musculoskeletal surgical procedures for osteoarthritis, rheumatoid arthritis, traumatic arthritis, avascular necrosis, nonunion of fractures of the femoral neck, sickle cell anemia, collagen disease, severe joint destruction secondary to trauma or other causes, and revision of previous arthroplasty procedures. The cement is also indicated for the fixation of pathological fractures with or without metallic fixation.

Contraindications

PMMA bone cement is contraindicated in the presence of active or incompletely treated infection which could involve the site where the cement is to be applied and in patients allergic to any of its components. These contraindications remain unchanged from those presented in the original petition.

Warnings

The warnings associated with the use of PMMA bone cement for the pathological fracture indication are the same as those outlined for the use of PMMA bone cement in total joint arthroplasty. These warnings were explained in the original petition and are bulleted below:

- Bone Cement Implantation Syndrome (BCIS)
    - Hypotension
    - Hypoxaemia
    - Cardiac Arrhythmias
    - Myocardial Infarction
    - Cardiac Arrest
    - Death
- Pulmonary Fat-Embolism
- Volatile, Flammable nature of Monomer
- Excessive Exposure to Monomer Vapers

- Persons wearing contact lenses should not be near or involved in the mixing of bone cement.

Precautions

The precautions as detailed in the original reclassification petition for bone cement used for total joint arthroplasty remain unchanged for bone cement used in the treatment of pathological fractures. The precautions are briefly outlined below:

- The liquid component has caused contact dermatitis in those handling and mixing them.
- The liquid component should not be allowed to come into contact with rubber or latex gloves.
- Inadequate fixation or unanticipated postoperative events may affect the cement-bone interface and lead to micromotion of cement against bone surface.
- Polymerization of the bone cement is an exothermic reaction which occurs while the cement is hardening in situ. The released heat may damage bone or other tissues surrounding the implant.
- Extrusion of the bone cement beyond the region of its intended application may occur.
- The safety of the bone cement in pregnant women or in children has not been established.
- The product should not be used after the expiration date printed on the package.
- The polymer component may be disposed in a landfill. The liquid component can be evaporated under a well-ventilated hood or absorbed by an inert material and transferred in a suitable container for deposition in a landfill.

Adverse Events

The use of PMMA bone cement for the treatment of pathological fractures yields no additional adverse events from those found for use in total joint arthroplasty. For completeness, the adverse events are stated in their entirety from the original petition.

Serious adverse events, some with fatal outcome, associated with the use of acrylic bone cements include myocardial infarction, cardiac arrest, cerebrovascular accident, pulmonary embolism.

The most frequent adverse reactions reported with acrylic bone cements are transitory fall in blood pressure, thrombophlebitis, hemorrhage and hematoma, loosening or displacement of the prosthesis, superficial or deep wound infection, trochanteric bursitis, and short-term cardiac conduction irregularities.

Other adverse reactions include heterotopic new bone formation and trochanteric separation. Other potential adverse events reported for acrylic bone cements include: pyrexia due to an allergy to the bone cement; hematuria, dysuria, bladder fistula, local

neuropathy, local vascular erosion and occlusion, and intestinal obstruction due to extrusion of the bone cement beyond the region of its intended application.

Alternate Practice and Procedures

Several factors go into the decision to treat a pathologic fracture and the best treatment to use, including the type of disease causing the lesion, extent of bone destruction, location of the fracture, and life expectancy and general condition of the patient. Alternatives to the use of PMMA bone cement in the treatment of pathologic fractures, include:

- nonoperative management with immobilization
- external plaster casting
- surgical external fixation devices
- internal fixation devices without the use of PMMA

SECTION III: IDENTIFICATION

The CFR currently defines poly(methyl methacrylate) bone cement as follows:

888.3027 Polymethylmethacrylate (PMMA) bone cement.

(a) *Identification.* Polymethylmethacrylate (PMMA) bone cement (luting agent) is a device intended to be implanted that is made from methylmethacrylate, polymethylmethacrylate, esters of methacrylic acid, or copolymers containing polymethylmethyacrylate and polystyrene. The device is intended for use in arthroplastic procedures of the hip, knee, and other joints for the fixation of polymer or metallic prosthetic implants to the living bone.

(b) *Classification.* Class III

The proposed CFR definition of Polymethyl methacrylate bone cement, as a class II device, follows:

Sec. 888.3027 Polymethylmethacrylate (PMMA) bone cement.

(a) *Identification.* Poly(methyl methacrylate) (PMMA) bone cement (luting agent) is a device intended to be implanted that is comprised of a liquid component consisting primarily of methyl methacrylate and a powder component composed primarily of poly(methyl methacrylate), and/or copolymers of methyl methacrylate and styrene or methyl acrylate. The device is intended for use in arthroplastic procedures of the hip, knee, and other joints for the fixation of polymer or metallic prosthetic implants to living bone. It is also intended for the fixation of pathological fractures with or without metallic fixation.

(b) *Classification.* Class II.

The proposed CFR definition presented in this amendment is the same as the proposed CFR definition originally submitted in the reclassification petition with the exception of the addition of the pathological fracture indication.

SECTION IV: SUMMARY OF REASONS FOR DOWNCLASSIFICATION

The pathological fractures indication was intended for inclusion in the original reclassification petition but was inadvertently omitted. The reasons for the reclassification of pathological fractures are consistent with those established in the original petition for total joint arthroplasty.

Restated, the documented clinical experience constitutes the new information, which is the basis for the Amendment to the Petition for downclassification of pathological fractures. The collective published literature is sufficient to provide reasonable assurance of the safety and effectiveness of PMMA bone cement used in pathological fractures. The literature also clearly establishes risk associated with the use of PMMA bone cement for this indication. The remaining sections of this petition amendment will establish that these known risks are controllable through adherence to standards and GMP/ QSR, appropriate pre-clinical testing, labeling and good surgical technique, and that PMMA bone cement may, therefore, be regulated by FDA as a Class II device.

SECTION V: CLINICAL RESULTS WITH PMMA BONE CEMENT

An overview of the clinical results for cemented hip, knee and shoulder arthroplasty was already discussed completely in the original Reclassification Petition (March 18, 1998) for Polymethylmethacrylate (PMMA) bone cement. The current overview will discuss the clinical results from the literature on the use of PMMA bone cement for the fixation of pathological fractures with and without metallic fixation.

INTRODUCTION

Bone cement has been used in orthopaedics for over 40 years for the fixation of joint replacement. Charnley (1) popularized the use of bone cement in the fixation of the Charnley total hip prosthesis starting in 1958. Since that time, bone cement has been used widely for prosthesis fixation at the hip. Later, bone cement was used for the fixation of total knee replacements and for the fixation of other joint prostheses. In giving the background to the decision to use bone cement, Charnley remarked that Knight had used the material previously to stabilize the spine and especially the cervical spine by molding it to the spinous processes and laminae. The procedure was still being used with good results (2).

Although bone cement has been most widely employed for prosthesis fixation, the nature of the material has lent itself for use in filling bone defects, in the reconstruction of skeletal members and for the support of fixation devices. Bone defects are created surgically in the excision of primary bone tumors or lesions of metastatic origin. Metastases are often found in the long bones of the upper or lower extremities and in vertebral bodies of the spine and elsewhere. The osteolytic nature of some tumors results in considerable bone destruction that necessitates the reconstruction of the bone structure itself. Fractures can occur through the bone tumor area, pathologic fractures. Bone cement is frequently needed to provide support for the osteosynthesis device used to reduce the fracture in order to avoid overloading and device failure. Support from bone cement may also be required in the treatment of fractures in osteoporotic bone.

There is a considerable amount of literature on the use of polymethylmethacrylate bone cement in applications involving the filling of bone defects and in the support of osteosynthesis devices. The literature ranges from discussion of anecdotal cases to the presentation of extensive series with long follow-up. The results have been quite satisfactory in that the objectives of pain relief, restoration of function and mobility and improvement in quality of life have been achieved for the lifetime of the patient. The publications usually do not identify the brand of bone cement employed.

PATHOLOGIC FRACTURES

There are five main categories of pathologic processes that develop fractures (3). The first category includes metastatic lesions of the bone. Malignant metastatic tumors are the most common neoplasm of the bone (4) and are the second most common cause of

pathologic fractures next to osteoporosis (3). The most common primary cancers that metastasize to the bone are breast, lung, renal, prostate, and thyroid cancers (4, 5, 6, 22). The second category includes systemic skeletal diseases, such as hyperparathyroidism and osteoporosis. The third category includes benign primary lesions in the bone caused by aneurysmal bone cysts, giant cell tumors, osteochondroma, and fibrous dysplasia, for examples. The fourth category includes malignant primary tumors of the bone such as myeloma, non-Hodgkin's lymphoma, and osteosarcoma. The fifth category includes other conditions, such as localized structural defects in the bone.

The majority of the published literature and the current overview primarily focus on the treatment of pathologic fractures resulting from metastatic lesions. These typically occur in people between the ages of 50 and 80 years old (4, 7). Pathologic fractures occur throughout the skeleton but primarily in the femoral neck, trochanteric region, femoral shaft, humerus, and in the cervical, thoracic and lumbar spine. Fractures occur most often in the spine and the pelvis, with about 10% occurring in long bones (8).

NONOPERATIVE MANAGEMENT OF PATHOLOGIC FRACTURES

Treatment of a pathologic fracture must be combined with the treatment of the underlying pathologic disease. Several factors go into the decision to treat a pathologic fracture and the best treatment to use, including the type of disease causing the lesion, extent of bone destruction, location of the fracture, and life expectancy and general condition of the patient. Treatment of a benign lesion could range from external plaster casting, to local surgical treatment, or a more extensive surgical excision of the lesion with internal fixation may be indicated. If the lesion is malignant, depending on the type of malignancy, treatment may include radiation and chemotherapy, as well. The goal of treatment for patients with pathologic fractures is to reduce pain as quickly as possible, restore function to the affected area, and to facilitate nursing care (9).

Nonoperative management of pathologic fractures includes long periods of immobilization while the fracture heals and significant amounts of narcotic analgesics used to treat the pain. This form of fracture fixation is typically not adequate and pain relief is generally not achieved (7). Treatment of the underlying pathologic disease typically requires radiation therapy, but radiation significantly inhibits and prolongs bone healing if rigid fixation of the bone is not achieved (8). The use of an external plaster cast may provide some immobilization, but radiation through the cast may result in significant skin breakdown. As a result of an unacceptably high complication rate, poor pain control, and low union rate with nonoperative methods, the standard method of dealing with pathologic fractures has been operative treatment (10).

SURGICAL MANAGEMENT OF PATHOLOGIC FRACTURES OF METASTATIC TUMORS

Pathologic fractures have been treated surgically with internal fixation since the 1950's (10). Radiation therapy is technically easier to do if there is no external fixation device

used; the patient has increased mobility with internal fixation. Internal fixation enhances the bony healing of patients while they are undergoing radiation therapy. Internal fixation also reduces or eliminates the pain related to the pathologic fracture and makes medical and nursing care easier. Internal fixation alone has its limitations, however, and can fail due to the diseased bone adjacent to the treated fracture. Early on, many patients were denied internal fixation due to the degree of their bone destruction, even though stability could not be achieved by external support or immobilization. As cancer treatments became more effective, patients began living longer and were counting more on the surgical benefits and durability of fracture fixation. This condition together with wider availability of PMMA bone cements during the 1960's led to the use of fracture augmentation with PMMA.

SURGICAL MANAGEMENT OF PATHOLOGIC FRACTURES WITH PMMA BONE CEMENT

Fixation techniques without the use of PMMA do not give adequate fixation in patients with extensive bone destruction. PMMA used in conjunction with internal fixation allows for the treatment of patients who would have previously been denied surgery. PMMA also enhances the stability of any fixation regardless of the degree of bone destruction. In cases where standard internal fixation techniques may be adequate, augmentation is greatly improved with the use of PMMA (17). PMMA is used in conjunction with intramedullary rod fixation; with screws and plates, it improves their fixation as well and provides the most optimum resistance to torsion (11). "Bone cement should be used in adequate amounts with any implant (endoprosthesis, nail or plate) which is used for reconstruction of a defect in a joint or a segment of a long bone in order to provide immediate stability."(5) PMMA is packed into defects in the bone following tissue resection to re-establish structural continuity (5, 7, 9, 22) and provides sufficiently rigid fixation of the fracture fragments to enhance the process of bone union after irradiation (22). The use of a strong column of PMMA that fills the space between the prosthetic or orthotic and the cortex of the bone provides the necessary fixation. PMMA provides immediate stability, allowing most patients to resume walking when the lower extremities are involved, restores function when the upper extremities are involved, and provides good pain relief in the majority of cases. The use of PMMA is not technically difficult in most cases but there is no standard guideline for how to use it in every case. PMMA augmentation of intramedullary fixation can be somewhat challenging. A new intramedullary rod was designed to allow PMMA to be injected through the rod to reduce this challenge (13). Due to the wide variety of presenting conditions of patients with pathological fractures, some amount of creativity is required in almost all instances (12, 22). PMMA is used to supplement the fixation in varying degrees, dependent on the location of the fracture and the amount of bone destruction, but also on the choice of metal fixation. On average, PMMA augmentation is utilized about 80-100% of the time (4, 7, 9).

The choice of internal fixation devices or prosthetic implants used is based on the location of the fracture and the amount of bone destruction. There are a wide variety of

internal fixation devices available for the treatment of pathologic fractures. Some of the basic systems employed in the various regions of the body include a nail and plate system, an endoprosthetic, or a dynamic hip screw in the femoral neck, head or trochanteric region (6, 9, 17), a nail and plate system or an intramedullary nail in the upper third of the femoral shaft, an intramedullary nail in the middle or lower third of the femoral shaft, and Rush pins or AO-plates used on the humerus (6, 9).

Pathological fractures of the spine causing significant pain and instability, particularly in the elderly and debilitated patient, can effectively be treated surgically with fusion and PMMA (14, 28). Operative treatment of the cervical spine may include a combination of hardware, bone cement, autograft and decompression. PMMA provides immediate stability of the construct so that external splinting while the bone graft is incorporating is not required (28). As in long bones, PMMA has also been used to fill significant bony destruction of the vertebrae.

Improved palliative care for patients with disseminated cancer has prolonged their lives but has increased the incidence of pathological fractures of the skeleton, especially fractures of the long bones. As mentioned previously, skeletal metastases are commonly found with primary tumors of the breast, prostate, thyroid, kidney and lung. Schulte et al (15) reported that 50 per cent of breast cancer patients developed skeletal metastases that were detected in life and that the level as detected at autopsy was 70 per cent. Treatment has been proposed not only for pathological fractures but also for impending fractures (4, 10, 17, 22). With the treatment of fractures or impending fractures an internal fixation device must often be used. The bone is weakened and provides insufficient support for the fixation device. The use of bone cement to fill defects and to provide support to the device has been found to prevent device fracture due to overloading and to avoid loss of purchase of screws in the weakened bone. Surgical treatment of the lesion has the goal of reducing or eliminating pain. The additional goal is to improve function and mobility of the patient so as to return the individual to the family setting. Overall, the intention is to increase the patient's quality of life.

A notable early description of the use of bone cement as an adjunct in internal fixation of malignant neoplastic fractures was given by Harrington et al (16). There were 30 patients with 31 actual and 2 impending fractures. The distribution of lesions was as follows: hip 9, femur 3 (intertrochanteric), femur 10 (subtrochanteric), femur 5 (shaft), humerus 2, tibia 3 and acetabulum 2. PMMA bone cement was used with a variety of internal fixation devices including IM nails, rods, intertrochanteric nails and total hip prostheses or hemiprostheses. Twenty-eight patients became ambulatory and there was only one case of failure of the fixation.

Also in this time frame, Sim et al (17) reported on the adjunctive use of methylmethacrylate cement to aid in the internal fixation of 35 pathological fractures and 16 imminent fractures. The distribution of the lesions was as follows: hip 25, femoral shaft 5, tibia 1, humerus 19 and ulna 1. The choice of reconstructive or internal fixation device was dictated by the location of the lesion. Effective fixation was achieved in all cases. Relief of pain was good in 38 patients, fair in 6 and poor in 7. There were no

failures of fixation and no significant complications attributable to the use of bone cement. According to the authors, satisfactory fixation would not have been possible in 20 cases without the use of cement and in 17 other patients the use of cement gave a considerably enhanced security of fixation. In a further publication, Sim et al (18) described 4 cases that illustrated the occurrence of pathological fractures from benign bone tumors, primary malignant bone tumors and the more common cause, metastatic bone tumors. The effectiveness of polymethylmethacrylate as an adjunct to treatment was highlighted for the latter type of pathological fracture. The authors stated that the patient should not be denied the benefit of internal fixation even when the bone destruction is extensive. Carlson and Adams (19) described 4 cases of the use of bone cement in the repair of pathological fractures. There were 2 hip fractures and 1 humerus fracture where cement was used as an adjunct to internal fixation and in the fourth case bone cement was used to reconstruct the bodies of two vertebrae that had been eroded by metastatic disease.

Eftekhar and Thurston (20) described 2 cases in which bone cement was used to supplement internal fixation. One patient had a mass in the intertrochanteric region and underwent curettage of the lesion and internal fixation with a nail/plate combination. The second patient had a large bone defect measuring some 8-cm that required bone cement to supplement the internal fixation. Both patients subsequently received 4500 r of cobalt 60. This raised the question of whether there were deleterious effects of radiation treatment on bone cement properties. The authors carried out a series of experiments irradiating cured bone cement up to a dose of 10,000 r and determined that irradiation had no effect on cement

Yablon and Paul (21) reported on the use of bone cement in 73 patients with 81 pathologic fractures that were treated by internal fixation. The purpose of using polymethylmethacrylate was to create rigid stabilization of the fracture when conventional means were inadequate. When an intramedullary device was used, the cement was placed within the intramedullary region first and the nail driven in place as the cement hardened. If the cement was to be placed in a circumferential manner, the internal fixation was applied first. The authors remarked that the wound was irrigated with cold saline to dissipate the heat generated during curing except for fractures of the humerus or spine where sterile crushed ice was used to protect the radial nerve and the spinal cord respectively. There were no failures of fixation and few complications. Survival varied but 12 patients were alive at more than 5 years post-surgery. Examples of patients were provided including a patient with metastases of the bodies of the second to sixth cervical vertebrae consequent to breast cancer. Bone cement was used to reconstruct the vertebral bodies. Although the dura mater was visible, damage appeared to be avoided by using sterile ice chips during cement curing. The patient had relief of pain and became ambulatory three days postoperatively. Yablon and Paul carried out canine studies on the effect of extensive cement placement on healing. Callus formation and healing were obtained if the cement was placed on one surface only. However, in cases of extensive bone destruction cement must be placed not only in the medullary canal but also circumferentially. Healing does not occur and so the fixation device could fail at

long times of follow-up. The life expectancy of these patients is usually not so long as to make this an issue.

A 1976 issue of the Journal of Bone and Joint Surgery carried further articles on the surgical treatment of pathological fractures. Harrington et al (22) extended their experience with the use of bone cement as an adjunct to internal fixation by reporting on 375 pathological fractures or impending fractures in 323 patients. The procedure was used in patients with a life expectancy of more than 3 months. There was a wide range of locations of the fractures or impending fractures: head and neck of the femur, acetabulum, pertrochanteric and subtrochanteric regions of the femur, shaft of the femur, tibia, humerus and ulna. Intramedullary rods, nails, nail/plate combinations, plates and prostheses were employed depending on the location and the extent of the fracture or threatened area. Many of the patients had subsequent radiotherapy. It was noted that the presence of methylmethacrylate did not affect the patients' response to the therapy and there was no evidence of an adverse effect of radiation on the cement itself. Of the 323 patients treated, there were only 4 cases of fixation failure. The use of bone cement effectively stabilized the fixation. Ninety-four per cent of patients who were ambulatory before the fracture regained the ability to walk. Eighty-five per cent had excellent or good pain relief and in only five per cent was the pain relief poor. The authors concluded that the use of polymethylmethacrylate had many advantages over conventional treatment where there was an unpredictable tendency to non-union with loss of fixation or collapse of the implant/bone construct. Douglass et al (23) described conventional treatment of pathological fractures i.e. fixation without the use of bone cement (bone cement was used in only 3 of 60 patients). Pain relief was good. However, the authors stated that they had now adopted the use of bone cement as an adjunct to fixation and had the impression that its use was beneficial. Zickel and Mouradian (24) studied the use of the Zickel nail for the treatment of pathological fractures and lesions of the subtrochanteric region of the femur. Polymethylmethacrylate was not used. The authors commented that there were cases of loss of position associated with extensive involvement of the femoral neck where methylmethacrylate might have been helpful. An editorial in the British Medical Journal (25) commented on the reports in the 1976 issue of the Journal of Bone and Joint Surgery. The editorial highlighted the use of bone cement in the treatment of pathological fractures. The use of surgical intervention for relief of pain and the description of techniques providing "humane and effective" action were welcomed.

Pollock and Marsh (26) described treatment of 15 patients with 16 pathological fractures. There were 12 lesions of the femur, 4 of the humerus and 1 bilateral. Rods, plates and nails were used as appropriate for internal fixation. Bone cement was used in all patients to increase the stability of the construct. There was one case of failure in which the intramedullary rod backed out. Pain relief was good and patients regained mobility. The authors noted that healing of the fracture would occur if the periosteal surface of the bone were left clear of cement. The use of methylmethacrylate in conjunction with internal fixation was an effective treatment for pathological fractures.

Habermann et al (27) provided an extensive series describing the treatment of 283 pathologic fractures and 23 impending fractures of the femur using prosthetic

replacement or internal fixation with or without the use of methylmethacrylate. The distribution of locations was as follows: femoral head, femoral neck, intertrochanteric region, subtrochanteric region, femoral shaft and supracondylar region. Implants included nail/plate devices, IM nails, condylar plates, endoprostheses and total hip prosthesis or custom device. In 64 per cent of cases, methylmethacrylate was used. The survival was 64 per cent and 51 per cent at 6 and 12 months respectively when cement was used and 47 per cent and 39 per cent in cases not receiving cement. Pain relief was good to excellent in 264 of 290 patients (97 per cent when cement was used and 83 per cent if there was no cement). There were 8 cases of fixation failure; 2 of these were with cement. There were 6 deep infections; 2 of these were with cement. The authors stated that the use of methylmethacrylate gave immediate functional stability and allowed early mobilization. Cement did not interfere with local radiation therapy and radiation did not reduce cement strength.

There have been more recent publications describing the use of bone cement as an adjunct to the fixation and treatment of pathological fractures. Fidler (28) reported on the results in 11 patients who had metastases in the cervical spine. A special plate was used to stabilize the spine with PMMA to supplement the fixation. Of the 11 patients, 6 received cement and 5 did not. If the life expectancy was less than 6 months or if there was no available autograft, then bone cement was used on both sides of the spine. Otherwise, cement was placed on one side and autograft on the other. Stability was increased if methylmethacrylate was used. Pain relief was good. Patients were able to get up a few days after surgery. There was one case of failure with cement due to collapse of the construct consequent to uncontrollable progression of the tumor. Fidler described the use of a fat-free graft with a layer of Gelfoam to protect the dura or nerve roots during cement curing; in addition, the cement was cooled with saline during setting. Gebhart et al (29) described the results of treatment in 31 patients with 24 pathological and 9 impending fractures. Most of the patients had lesions either in the femur or the humerus. The devices employed included total hip and knee prostheses, a megaprosthesis, a bicentric prosthesis and intramedullary nails. Internal fixation was used for 15 lesions and produced a rapid, rigid fixation accelerating bone healing. Van Geffen et al (30) commented that about 10 per cent of patients with skeletal metastases would develop a pathological fracture with the vertebrae, femur, pelvis and humerus most at risk due to the greatest loading. A retrospective study of 116 patients with 152 impending pathological fractures was described. A variety of factors were evaluated including the use of PMMA that was used in 55 per cent of the operations. Pain relief was no different whether or not cement was used. The use of cement did not lead to additional complications. Since function was better when methylmethacrylate was used, the authors recommended that cement be employed. Mahaisavariya et al (31) described the use of the AO nail for subtrochanteric fractures with the adjuvant use of bone cement for added stability in 2 cases of pathologic fracture as distinct from the use of the nail without cement for patients who had fractures from road traffic accidents. Again, this highlights that cement is used only in those instances when the construct is insufficiently stable either due to loss of bone or due to weakness of the bone itself.

The use of methylmethacrylate bone cement has become a standard in the treatment of pathologic fractures and impending fractures when additional stabilization of the internal fixation device is required (32). In correspondence to the Journal, Zickel (33) took exception to the recommendation that bone cement be used routinely. In a rebuttal, Aaron (34) cited studies demonstrating the utility of methylmethacrylate in providing support for internal fixation. The difference appears to be one of perception rather than reality. For specific types of tumors and locations, methylmethacrylate may not be needed. The overzealous use of cement should be avoided. However, methylmethacrylate has been demonstrated to be a valuable adjunct to internal fixation when additional support is needed.

THE USE OF POLYMETHYLMETHACRYLATE FOR OTHER PATHOLOGIC FRACTURES

Several authors have presented their experiences on the use of methylmethacrylate as an adjunct to internal fixation in osteoporotic patients (35, 7, 36, 37, 38, 39). The principles in employing bone cement for patients with fractures through osteoporotic bone are to provide support to the internal fixation device to avoid overloading and failure and to allow early weight bearing. The use of cement was reported to be a valuable adjunct to fracture treatment in the elderly, debilitated, osteoporotic patient. Benum (37) stated that the fractures could not have been stabilized without the use of bone cement. It provided immediate fracture stability with an excellent prospect for healing while avoiding the complications of implant failure and bed confinement, which are frequently fatal in this group of patients.

As mentioned in the beginning of this overview, other pathologic processes also developed fractures. The literature is full of case studies and small population studies on a wide variety of pathologic conditions that PMMA has been used for the treatment of. These conditions range from rare bone diseases such as Hydatid disease, to fibrous dysplasia, chondroblastomoma, and giant cell tumors of the bone. Treatment frequently involves curettage of the lesion and PMMA cement packaging. Depending on the size and location of the lesion, metal hardware reinforcement may be used. Additional adjuvant procedures may also include chemical or thermal cauterization, bone grafting, or cryosurgery. All seem to report satisfactory results with the use of PMMA.

DISCUSSION

Bone cement provides many advantages especially with patients having a limited life expectancy in that it provides immediate support that allows mobility and weight bearing with or without an internal fixation device. The aim has been to relieve pain, to restore mobility and to increase quality of life. Patients are less dependent, can often be returned to the family setting and can be treated further as out patients rather than being confined to the hospital. In all these regards, the use of bone cement has been a success.

Tumors of the long bones may be primary in origin but are more likely to be metastases due to cancers of the breast, prostate, lung, thyroid and kidney among others. Patients may have metastatic lesions in other locations including the pelvis and spine in addition to those in the long bones. Patients may have more than one bone lesion occurring simultaneously or sequentially if life expectancy is sufficient; breast cancer patients are among those with sufficient life expectancy. The objectives of surgical intervention are those given above, namely to reduce pain, restore function and increase quality of life. Many of the bone lesions are found as a consequence of pathological fracture and must be dealt with on that basis. A wide variety of options are available ranging from internal fixation (plates, nail/plate devices and intramedullary devices) to the use of endoprostheses, total joint prostheses and custom devices. Methylmethacrylate has been used for direct prosthesis fixation, to provide support for internal fixation devices or to rebuild bony structures such as vertebral bodies destroyed by osteolytic tumor effects. The results of these interventions have been widely reported. The outcomes have been excellent in the context of the underlying disease with relief of pain and restoration of function and mobility. The use of bone cement has become widely accepted for those situations where immediate stability is needed consequent to bone loss or loss of general bone quality. The use of cement does not preclude subsequent radiotherapy and cement does not interfere with the response of the patient. Radiation does not have adverse effects on cement itself. Complications have been reported as minimal. Again, there is the issue of thermal effects of curing of cement. This has been addressed in a variety of ways by the surgeon. At the spine the situation is especially problematic due to the proximity of the dura or spinal cord. Even here, complications have been minimized or eliminated through use of judicious cooling and interpositional materials. The use of bone cement is safe and effective.

Osteoporosis is an increasing concern when coupled with increased life expectancy of the population. Some surgeons regard fractures through osteoporotic bone as akin to pathological fractures. Bone cement has been used in elderly patients with comminuted intertrochanteric fractures, supracondylar femoral fractures and fractures in the distal third of the femur as a way of stabilizing the internal fixation device. Again, the aim has been to minimize complications from excessive bed confinement e.g. pneumonia and bed ulcers, and to restore mobility and quality of life through reduced dependency. The reports indeed show that the employment of cement does allow early weight bearing. The use of methylmethacrylate may be especially appropriate in those patients with limited life expectancy due to comorbidities.

CONCLUSION

Metastases frequently occur in bone from cancers of the breast, prostate, thyroid, lung, and kidney and from other cancers. Pathological fractures can be devastating to already debilitated patients. Some 30 years ago, it was shown that such fractures could be effectively treated by using bone cement to provide support to the internal fixation device or other type of prosthesis. The goal again was to allow early mobility and weight bearing, to relieve pain and to increase the quality of life of the patient. Bone cement has

been used in the long bones, the pelvis, the spine and at other locations. Even with proximity of the dura mater or nerves, cement can be cured *in situ*, using appropriate measures as described in the literature. Methylmethacrylate has been used to provide support to many types of internal fixation devices including intramedullary nails, nail/plate constructs and plates and screws. Cement has been used to build up vertebral bodies destroyed through the osteolytic action of tumors. The reports indicate that the use of bone cement is safe and that it provides the surgeon with options allowing an effective treatment for this type of patient.

The reports in the literature demonstrate that methylmethacrylate can be used effectively to support internal fixation devices even with severely osteoporotic bone. Cement has been shown to be safe and is part of an effective treatment protocol for these types of fractures in patients with advanced osteoporosis.

No meaningful comparisons can be made from the literature between internal fixation with PMMA and without PMMA. Typically cases done without PMMA had significantly less bone destruction and many of the cases done with PMMA would not have been attempted without it (12). Bone cement provides options not otherwise available. Mobility can be restored to upper extremities. The use of methylmethacrylate provides stability in the femur and tibia that would not be achieved in the absence of cement, allowing early weight bearing and ambulation. Stability may also be achieved in the spine. Pain may be reduced for patients with metastatic lesions of bone. Together with the low level of complications, cement provides a safe and effective addition to the armamentarium of the surgeon.

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