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Systemic effects of polymethylmethacrylate

Increased serum levels of gamma-glutamyltranspeptidase following arthroplasty

This study dealt with the effects of polymethylmethacrylate (PMMA) in total hip and knee arthroplasty patients on serum gamma-glutamyltranspeptidase GGTP levels. Patients undergoing open reduction and internal fixation of hip fractures served as control patients. Results of this study showed that 11 of 90 total hip patients and seven of 23 total knee patients had abnormally elevated GGTP levels at 5 and 10 days postoperatively. Abnormal elevations of GGTP levels in 40 hip fracture patients, however, were not noted. Clinical findings in this study included the observations that three of the 11 hip patients with elevated GGTP levels concurrently had symptoms of anorexia, nausea and/or vomiting, along with spiking temperatures in the postoperative period. These symptoms generally occurred by 5 days following surgery and resolved uneventfully by 10 days postoperatively. Likewise, two of the seven knee patients with elevated GGTP levels in the postoperative period had the symptoms described above. No symptoms were reported from the hip fracture patients.

Merrill A. Ritter
Terence J. Gioe
Jon M. Sieber

Medical Research Department, Methodist Hospital of Indiana, Inc. and Indiana University School of Medicine, Indianapolis, USA

Correspondence:
1815 N. Capitol Avenue, Suite 214, Indianapolis, IN 46202, USA

Polymethylmethacrylate (PMMA) functions primarily as a grouting agent in the stabilization of component parts of prostheses. Preparation of PMMA for implantation requires a polymerization process which can produce local temperatures above 56°C, the body protein coagulation point, though adverse effects are rarely seen *in vivo* (Biehl et al. 1979, Charnley 1975, Feith 1975, Miller et al. 1976). If preoperative fluid volume is not regulated, a peripheral vasodilation leading to a drop in blood pressure may be seen secondarily to the local effect of the monomer (Ellis & Mulvein 1974, Kim & Ritter 1972). Any direct effect of the absorbed monomer on the postoperative total hip replacement patient has been virtually absolved by the extensive studies of Feith (1975) and Smith & Turner (1973).

Nevertheless, some patients have revealed postoperative serum enzyme alterations following PMMA use (Burton 1974). Are the postoperative alterations in various serum enzyme levels due to the utilization of PMMA, or possibly only the result of the extensive surgical intervention and therefore a normal postoperative occurrence?

The purpose of this study was to evaluate postoperative alterations of the venous blood and the clinical course of a number of consecutive total hip arthroplasty patients and a smaller number of total knee arthroplasties in an attempt to answer this question, and to determine what role, if any, PMMA plays in abnormal fluctuations in blood chemistry.

Patients and methods

In 1980, 90 consecutive total hip arthroplasty patients of the senior author, using Simplex P bone cement, were sampled for gamma-glutamyltranspeptidase (GGTP) 1 day prior to surgery and at the fifth and tenth postoperative days. GGTP, an enzyme quite specific for alterations in liver function, has normal values of 3–30 IU/ml at our laboratory. Likewise, enzyme levels of GGTP were obtained for 23 consecutive total knee arthroplasties and 40 consecutive unilateral hip fractures. The hip fractures, all of which utilized open reduction and internal fixa-

tion, included several varieties of fracture and served as a reasonable control of operative trauma without the use of PMMA. Inclusion of the total knee arthroplasty patients allowed us to delineate further the effects of operative trauma and quantity of PMMA used (both factors of which are less in knees than in hips) on serum enzyme elevations. All total hip and knee replacements and fractured hips were treated with 2 days of prophylactic cephamandol.

The clinical course of all patients in this study was closely followed, with particular attention being paid to those patients complaining of nausea, anorexia and spiking temperatures in the postoperative period.

Results

The results of assaying for GGTP in serum preoperatively and at 5 and 10 days postoperatively are displayed in Table 1. Of 90 consecutive hip arthroplasties examined, 11 showed elevation of GGTP above normal levels. The mean elevation above preoperative levels was 300 per cent at the fifth postoperative day. Among the 40 control patients with hip fractures, GGTP values remained within normal limits at all points, averaging 11.5 IU/ml preoperatively, 17.3 IU/ml at 5 days postoperatively, and 19.4 IU/ml at 10 days postoperatively. Examination of 23 consecutive total condylar knee arthroplasties revealed GGTP elevation in seven patients (30.4 per cent), averaging 338 per cent above preoperative levels at the fifth postoperative day. These levels continued to climb until the tenth postoperative day, though at a more reasonable rate.

Clinical observations made during this study revealed that three of the 90 total hip subjects developed symptoms of anorexia, nausea and/or vomiting and occasionally spiking temperatures ($\leq$102°F) from approximately the fifth through the tenth postoperative day, coupled with abnormally elevated GGTP levels. Likewise, two of the 23 total knee arthroplasty patients reported similar postoperative symptoms and these patients were also found to be among the seven knee patients with abnormally elevated GGTP levels. Also, no patient had the above symptoms for more than 5–7 days without abnormal enzyme elevations. Finally, none of the control hip fracture patients in this study were noted to have any of the postoperative symptoms described previously.

This syndrome can best be illustrated by a 56-year-old black female who underwent a right total condylar knee replacement for osteoarthritis secondary to osteonecrosis. Spiking temperatures to 100.4°F were noted until the tenth day postoperatively. A GGTP value of 53 obtained on the fifth postoperative day had risen to 75 by the tenth day following surgery and was gradually found to decrease in the next few days. The patient complained of nausea and anorexia through the tenth postoperative day. The patient is now asymptomatic 4 years postoperatively.

Table 1. GGTP values (IU/ml) for those total hip and total knee arthroplasties with normal preoperative and elevated postoperative levels compared to the normal, pre- and postoperative levels of all the fractured hip patients.

	Total	Bilateral	Unilateral
Knee arthroplasties	7	7	3
Preoperative	13.5	11.7	16.0
Five days	59.1	58.2	60.3
Ten days	73.8	62.0	89.5
Hip arthroplasties	11	3	8
Preoperative	21.4	20.0	25.2
Five days	85.6	118	74.8
Ten days	83.7	101	79.5
Fractured hip	40	–	40
Preoperative	11.5	–	11.5
Five days	17.3	–	17.3
Ten days	19.4	–	19.4

Discussion

Several authors have examined the duration, peak and circumstances surrounding serum enzyme elevations following various surgical operations. In 1974, Burton reported on the alterations of serum enzyme levels following the use of PMMA. Our investigation into this subject was initiated after noticing patients developing abnormal fluctuations in GGTP levels postoperatively with concurrent clinical symptoms previously mentioned. Obviously, several factors must be dealt with in any attempt to implicate a causative agent of such serum enzyme elevations and persistent clinical symptoms. One of the biggest questions concerned

the effect of orthopedic procedures involving extensive skeletal muscle trauma on enzyme levels.

Although the specificity is not absolute, GGTP is not generally elevated in muscle disease or routine surgical trauma as are the transaminases, and is not subject to errors in measurement as the result of sample hemolysis (Rosalki 1975). Disease categories of nonhepatic origin resulting in elevated GGTP levels include myocardial disorders, diabetes, epilepsy, and other patients receiving long-term enzyme-inducing drug therapy (Rosalki 1975). These diagnoses were ruled out as a matter of course in this study. Reasonably similar levels of operative trauma without the use of PMMA utilized in repair of hip fractures did not result in significant elevation of postoperative GGTP levels. Elevation of GGTP levels in the cases we have described is thus most likely the result of hepatocellular involvement.

While liver biopsy would provide the most conclusive proof of hepatic involvement in the serum enzyme elevations noted here, patient consent for such a procedure is notoriously low. Measurement of GGTP serum levels is the most promising alternative. Rosalki (1975) found GGTP to be "more frequently, and more sensitively elevated than any other commonly used laboratory test for liver disorder" and concluded that such sensitivity and stability make the GGTP measurement "the best available screening test for liver disease".

The elevated spiking temperatures, nausea, and anorexia seen here in a fraction (3.6 per cent) of the clinical studies, in addition to the evidence provided by the GGTP studies, indicate probable hepatic involvement. Lacking other feasible explanations, we suggest that PMMA may be the cause of the serum enzyme elevations and concurrent clinical findings. We refer to this syndrome as "cement hepatitis". The mechanism of this reaction to PMMA would seem to involve an idiosyncratic reaction, as compared to a dose-related response, owing to the higher percentage of knee patients with GGTP elevations despite the use of less PMMA in knee procedures.

The significance of the findings in this study is readily apparent if indeed PMMA usage is the causative factor for the symptoms noted. The normal total joint patient presenting with the above complaints would be suspected of harboring an infection and the joint might then be tapped. This practice, in light of our findings, seems to be a rather painful and unnecessary risk for the patient. Our experience has been that peak GGTP levels occur by approximately 10 days postoperatively and by 14 days GGTP levels have neared renormalization along with resolution of symptoms. Therefore, when an elevated GGTP is noted, a more judicious approach of monitoring GGTP levels for 2 weeks postoperatively may prove to be a more reasonable solution for this clinical presentation.

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