INTRODUCTION

In orthopedic surgery, the use of polymethylmethacrylate (PMMA) bone cement has proven effective in stabilizing implants and filling dead space created in the treatment of infection after osteosynthesis. In 1970, Buchholz and Engelbrecht were the first to describe their use associated with antibiotics followed by publications showing the efficacy of this association in the treatment of orthopedic infections. Its advantages compared to oral or intravenous antibiotic therapy include the release of local antibiotics in higher concentrations, relative lower serum level, and consequent reduction in toxicity associated with the use of systemic antibiotics. There is no consensus in the literature regarding the time for the removal of the spacer, and few studies describe the effects of its prolonged retention of the same. The aim of this study is to evaluate the clinical results of patients with prolonged retention of the same. Methods: Patients selected were diagnosed with post-osteosynthesis infection and/or osteomyelitis and were submitted to treatment using an orthopedic cement spacer (polymethylmethacrylate) with vancomycin, retaining it for a period of more than 12 months. They were clinically evaluated to determine the presence of local or systemic infectious signs via hemogram, investigations of inflammatory markers, liver, renal and, with radiographic control. Results: Eighteen patients were included in the study. The mean retention time of the spacer was 30.4 months (15 - 61 months). No patient had clinical signs of local or systemic infectious relapse at the time of evaluation. Seven patients (39%) presented non-disabling pain in the operated limb. Seventeen patients (94%) presented a reduction in C-reactive protein values compared to the preoperative period. Radiographically, no migration, no spacer failure, or bone sequestration occurred. Conclusion: In this retrospective case series, cement spacer retention with vancomycin for more than 12 months was associated with good clinical results, without relapse of the infectious condition.

Keywords: Osteomyelitis, Polymethyl Methacrylate, Anti-Bacterial Agents.

ABSTRACT

Objective: There is no consensus in the literature regarding the time taken to remove antibiotic spacers in the treatment of bone infections. The aim of this study is to evaluate the clinical results of patients with prolonged retention of the same. Methods: Patients selected were diagnosed with post-osteosynthesis infection and/or osteomyelitis and were submitted to treatment using an orthopedic cement spacer (polymethylmethacrylate) with vancomycin, retaining it for a period of more than 12 months. They were clinically evaluated to determine the presence of local or systemic infectious signs via hemogram, investigations of inflammatory markers, liver, renal and, with radiographic control. Results: Eighteen patients were included in the study. The mean retention time of the spacer was 30.4 months (15 - 61 months). No patient had clinical signs of local or systemic infectious relapse at the time of evaluation. Seven patients (39%) presented non-disabling pain in the operated limb. Seventeen patients (94%) presented a reduction in C-reactive protein values compared to the preoperative period. Radiographically, no migration, no spacer failure, or bone sequestration occurred. Conclusion: In this retrospective case series, cement spacer retention with vancomycin for more than 12 months was associated with good clinical results, without relapse of the infectious condition.

Keywords: Osteomyelitis, Polymethyl Methacrylate, Anti-Bacterial Agents.

RESUMO

Objetivos: Na literatura não há consenso em relação ao tempo para a retirada dos espaçadores com antibiótico no tratamento das infecções ósseas. O objetivo deste estudo é avaliar os resultados clínicos dos pacientes com retenção prolongada dos mesmos. Métodos: Foram selecionados pacientes com infecção pós-osteossíntese e/ou osteomielite submetidos a colocação de espaçador de cimento ortopédico (polimetilmetacrilato) com vancomicina que retiveram o mesmo por período superior a 12 meses. Os pacientes foram avaliados clinicamente quanto à presença de sinais infecciosos locais ou sistêmicos, laboratorialmente com hemograma, marcadores inflamatórios, função hepática, renal e radiograficamente. Resultados: Dez oito pacientes foram incluídos no estudo. O tempo médio de retenção do espaçador foi de 30,4 meses (15 a 61 meses). Nenhum paciente apresentou sinais clínicos de recidiva infecciosa local ou sistêmica no momento da avaliação. Sete pacientes (39%) apresentaram dor não incapacitante no membro operado. Dezessete pacientes (94%) apresentaram redução nos valores da proteína C reativa comparativamente ao período pré-operatório. Radiograficamente, não houve migração, falha do espaçador ou identificação de sequestro ósseo em nenhum caso. Conclusão: Nessa série de casos retrospectiva, a retenção do espaçador de cimento com vancomicina por mais de 12 meses foi associada a bons resultados clínicos, sem recidiva do quadro infeccioso.

Descritores: Osteomielite. Polimetil Metacrilato. Antibacteriano.

INTRODUCTION

In orthopedic surgery, the use of polymethylmethacrylate (PMMA) bone cement has proven effective in stabilizing implants and filling dead space created in the treatment of infection after osteosynthesis. In 1970, Buchholz and Engelbrecht were the first to describe their use associated with antibiotics followed by publications showing the efficacy of this association in the treatment of orthopedic infections. Its advantages compared to oral or intravenous antibiotic therapy include the release of local antibiotics in higher concentrations, relative lower serum level, and consequent reduction in toxicity associated with the use of systemic antibiotics. There is no consensus in the literature regarding the time for the removal of the spacer, and few studies describe the effects of its prolonged retention of the same. The aim of this study is to evaluate the clinical results of patients with prolonged retention of the same. Methods: Patients selected were diagnosed with post-osteosynthesis infection and/or osteomyelitis and were submitted to treatment using an orthopedic cement spacer (polymethylmethacrylate) with vancomycin, retaining it for a period of more than 12 months. They were clinically evaluated to determine the presence of local or systemic infectious signs via hemogram, investigations of inflammatory markers, liver, renal and, with radiographic control. Results: Eighteen patients were included in the study. The mean retention time of the spacer was 30.4 months (15 - 61 months). No patient had clinical signs of local or systemic infectious relapse at the time of evaluation. Seven patients (39%) presented non-disabling pain in the operated limb. Seventeen patients (94%) presented a reduction in C-reactive protein values compared to the preoperative period. Radiographically, no migration, no spacer failure, or bone sequestration occurred. Conclusion: In this retrospective case series, cement spacer retention with vancomycin for more than 12 months was associated with good clinical results, without relapse of the infectious condition.

Keywords: Osteomyelitis, Polymethyl Methacrylate, Anti-Bacterial Agents.

RESUMO

Objetivos: Na literatura não há consenso em relação ao tempo para a retirada dos espaçadores com antibiótico no tratamento das infecções ósseas. O objetivo deste estudo é avaliar os resultados clínicos dos pacientes com retenção prolongada dos mesmos. Métodos: Foram selecionados pacientes com infecção pós-osteossíntese e/ou osteomielite submetidos a colocação de espaçador de cimento ortopédico (polimetilmetacrilato) com vancomicina que retiveram o mesmo por período superior a 12 meses. Os pacientes foram avaliados clinicamente quanto à presença de sinais infecciosos locais ou sistêmicos, laboratorialmente com hemograma, marcadores inflamatórios, função hepática, renal e radiograficamente. Resultados: Dez oito pacientes foram incluídos no estudo. O tempo médio de retenção do espaçador foi de 30,4 meses (15 a 61 meses). Nenhum paciente apresentou sinais clínicos de recidiva infecciosa local ou sistêmica no momento da avaliação. Sete pacientes (39%) apresentaram dor não incapacitante no membro operado. Dezessete pacientes (94%) apresentaram redução nos valores da proteína C reativa comparativamente ao período pré-operatório. Radiograficamente, não houve migração, falha do espaçador ou identificação de sequestro ósseo em nenhum caso. Conclusão: Nessa série de casos retrospectiva, a retenção do espaçador de cimento com vancomicina por mais de 12 meses foi associada a bons resultados clínicos, sem recidiva do quadro infeccioso.

Descritores: Osteomielite. Polimetil Metacrilato. Antibacteriano.
RESULTS

In total, 18 patients met the selection criteria. The mean age was 39.9 (range: 18 - 61) years; 13 patients (72.2%) were male and five patients (27.8%) were female (Table 1). Half of the patients evaluated had undergone surgery due to Chronic Hematogenous Osteomyelitis, and the other half were operated due to a postoperative infection (Table 2). Five patients (27.8%) contracted an infection after an automobile accident, three (16.7%) after falls and one (5.6%) after a firearm injury. The mean retention time of the spacers was 30.4 months, ranging from 15 to 61 months, with 12 patients (66.7%) with diaphyseal spacers and six with pearl necklaces (33.3%). Eleven patients underwent surgery on the femur (61.1%), six on the tibia (33.3%), and one on the humerus (5.6%). Three patients were diagnosed with systemic arterial hypertension (16.7%) and two with diabetes mellitus (11.1%). Of the 18 patients, 11 (61.1%) declared to be social drinkers and three (16.7%) were smokers.

### Table 1. Demographic and clinical characteristics of selected patients.

| Case | Age | Gender | Diagnostic | VAS | Bacteria | PCR (mg/L) |
|------|-----|--------|------------|-----|----------|------------|
| 1    | 41  | COM    | 6/10       | Streptococcus anginosus | 155.0 - 10.7 |
| 2    | 52  | COM    | 2/10       | S. aureus/S. epidermidis | 329.1 - 1.6 |
| 3    | 25  | COM    | 0/10       | Serratia marcescens | 533.0 - 0.7 |
| 4    | 59  | COM    | 0/10       | P. aeruginosa/K. pneumoniae | 7.6 - 20.9 |
| 5    | 18  | COM    | 0/10       | S. epidermidis | 21.0 - 1.4 |
| 6    | 39  | COM    | 0/10       | S. aureus/S. epidermidis | 410.6 - 2.0 |
| 7    | 31  | COM    | 0/10       | S. epidermidis | 108.4 - 14.2 |
| 8    | 61  | COM    | 0/10       | S. aureus | 17.8 - 7.5 |
| 9    | 18  | COM    | 0/10       | S. aureus | 94.0 - 1.5 |
| 10   | 32  | POI    | 6/10       | Staphylococcus lugdunensis | 29.8 - 1.5 |
| 11   | 53  | POI    | 6/10       | S. aureus | 45.0 - 1.3 |
| 12   | 50  | POI    | 3/10       | S. aureus | 40.7 - 3.5 |
| 13   | 51  | POI    | 3/10       | S. aureus | 110.0 - 21.8 |
| 14   | 47  | POI    | 1/10       | S. aureus | 79.9 - 11.0 |
| 15   | 38  | POI    | 0/10       | Proteus mirabilis | 8.3 - 2.1 |
| 16   | 35  | POI    | 0/10       | Peptostreptococcus anaerobius | 95.1 - 9.3 |
| 17   | 48  | POI    | 0/10       | S. aureus | 13.9 - 3.0 |
| 18   | 20  | POI    | 0/10       | S. aureus | 271.4 - 6.3 |

Abbreviation: VAS, Visual Analogue Scale of Pain; COM, Chronic Osteomyelitis; POI, Postoperative Infection. * Values in the presence of infection and during outpatient return after 12 months of spacer retention. Reference value: <5.0 mg/L.
In cases of chronic hematogenous osteomyelitis, Staphylococcus aureus was the most prevalent bacteria isolated, affecting four patients (44.4%). Only one patient in this group showed an increase in the C-reactive protein when comparing the results in the presence of infection and during the outpatient return after 12 months of retention. S. aureus was also responsible for six postoperative infections (66.7%), with all cases showing a decrease in the C-reactive protein (Table 2). No change was observed when comparing the results of the other laboratory tests requested (complete blood count, AST, ALT, alkaline phosphatase, gamma-GT, total bilirubin and fractions, albumin, coagulogram). All of the above exam results were within the reference values. No signs of new fractures of infectious recurrence, such as thickening of the periosteum or bone sequestration, were observed in any of the patients. In fracture cases, Lane and Sandhu’s criteria were used, and a maximum score was assigned for each fracture, with total bone formation, absence of fracture line and cortical remodeling.

**DISCUSSION**

The primary objective of this study was to clinically evaluate and identify possible late complications (clinical, laboratory or radiographic) of patients with retention of the PMMA spacer with vancomycin after a minimum period of 12 months. The initial hypothesis of the study was that retaining the PMMA spacer with vancomycin for more than 12 months in patients with good clinical evolution and control of local infectious signs can be tolerated by a significant number of patients, without negative clinical repercussions in the long term. The main disadvantage in the use of PMMA is the need to remove the spacer, as it can act as a growth medium for resistant organisms.

One of the pioneering studies on this subject was conducted by Kendall et al., who analyzed an in vitro model associating acrylic cement with antibiotics. Viable organisms were found in cement after 96 hours and, for this reason, the authors began to recommend the cautious use of cement in clinical practice. However, the combination of antibiotics with PMMA in the treatment of infected or at-risk orthopedic lesions has been shown to reduce infection rates, both in animals and clinical studies. In a retrospective study, Selhi et al. described the retention of intramedullary implants with bone cement and antibiotics for a period ranging from 6 weeks to 22 months (mean, 10.6 months) with satisfactory results in the treatment of infected non-union fractures. The authors mention studies that retained implants for up to 753 days without any complications other than implant breakage in a single patient. Similarly, Paley et al. followed-up on patients with intramedullary bone cement and antibiotic implants for a period ranging from 32 to 48 months (mean 40.9 months), without recurrent infections in this interval. Following the selection criteria, 18 patients with spacer retention with an interval ranging from 15 to 61 months, with a mean of 30.4 months (SD = 13.36) were selected. In all cases, the patients chose to remain with the spacers and not to be subjected to a new surgical procedure for their removal. It was found that none of the patients had persistent drainage of the surgical wound, dehiscence of the surgical wound, formation of seroma near the site of bone cement insertion, fever, or thromboembolic episodes.

**CONCLUSION**

This study showed that patients with vancomycin cement spacers with good clinical evolution throughout more than 12 months could maintain a controlled infectious condition with spacer retention, and no complications or adverse events directly associated with spacer retention were identified.
REFERENCES

1. Dusane DH, Diamond SM, Knecht CS, Farrar NR, Peters CW, Howlin RP, et al. Effects of loading concentration, blood and synovial fluid on antibiotic release and anti-biofilm activity of bone cement beads. J Control Release. 2017;248:24–32.

2. McConoughey SJ, Howlin RP, Wiseman J, Stoodley P, Calhoun JH. Comparing PMMA and calcium sulfate as carriers for the local delivery of antibiotics to infected surgical sites. J Biomed Mater Res B Appl Biomater. 2015;103(4):870–7.

3. Oh EJ, Oh SH, Lee IS, Kwon OS, Lee JH. Antibiotic-eluting hydrophilized PMMA bone cement with prolonged bactericidal effect for the treatment of osteomyelitis. J Biomat Appl. 2016;30(10):1534–44.

4. Luo S, Jiang T, Yang Y, Yang X, Zhao J. Combination therapy with vancomycin loaded calcium sulfate and vancomycin-loaded PMMA in the treatment of chronic osteomyelitis. BMC Musculoskelet Disord. 2016;17(1):502.

5. Zalavras CG, Patzakis MJ, Holton P. Local antibiotic therapy in the treatment of open fractures and osteomyelitis. Clin Orthop Relat Res. 2004;(427):86–93.

6. Swearingen MC, Granger JF, Sullivan A, Stoodley P. Elution of antibiotics from poly(methyl methacrylate) bone cement after extended implantation does not necessarily clear the infection despite susceptibility of the clinical isolates. Pathog Dis. 2016;74(1):ftv103.

7. Kluin OS, van der Mei HC, Busscher HJ, Neut D. Biodegradable vs non-biodegradable antibiotic delivery devices in the treatment of osteomyelitis. Expert Opin Drug Deliv. 2013;10(3):341–51.

8. Elmarsafi T, Oliver NG, Steinberg JS, Evans KK, Attinger CE, Kim PJ. Long-Term Outcomes of Permanent Cement Spacers in the Infected Foot. J Foot Ankle Surg. 2017;56(2):287–90.

9. Hake ME, Young H, Hak DJ, Stahel PF, Hammerberg EM, Mauffrey C. Local antibiotic therapy strategies in orthopaedic trauma: Practical tips and tricks and review of the literature. Injury. 2015;46(8):1447–56.

10. Kendall RW, Duncan CP, Smith JA, Ngui-Yen JH. Persistence of bacteria on antibiotic loaded acrylic deposits. A reason for caution. Clin Orthop Relat Res. 1996;(329):273–80.

11. Selhi HS, Mahindra P, Yamin M, Jain D, De Long WG Jr, Singh J. Outcome in patients with an infected nonunion of the long bones treated with a reinforced antibiotic bone cement rod. J Orthop Trauma. 2012;26(3):184–8.

12. Paley D, Herzenberg JE. Intramedullary infections treated with antibiotic cement rods: preliminary results in nine cases. J Orthop Trauma. 2002;16(10):723–9.

13. Amin TJ, Lamping JW, Hendricks KJ, McIlff TE. Increasing the Elution of Vancomycin from High-Dose Antibiotic-Loaded Bone Cement. J Bone Joint Surg Am. 2012;94(21):1946–51.

14. Dovas S, Liakopoulos V, Papatheodorou L, Chronopoulou I, Papavasiliou V, Atmatzidis E, et al. Acute renal failure after antibiotic-impregnated bone cement treatment of an infected total knee arthroplasty. Clin Nephrol. 2008;69(3):207–12.