Rev Bras Cir Cardiovasc 2012;27(3):392-400

Biocompatibility of Ricinus comunnis polymer compared to titanium implant used in artificial hearts. Experimental study in guinea pigs

Biocompatibilidade do polímero da mamona comparada ao implante de titânio para corações artificiais. Estudo experimental em cobaias

Luiz Fernando Kubrusly[1], Yorgos Luiz Santos de Salles Graça[2], Enéas Eduardo Sucharski[3], Ana Cristina Lira Sobral[4], Marcia Olandoski[5], Fernando Bermudez Kubrusly[6]

DOI: 10.5935/1678-9741.20120067

RBCCV 44205-1398

Abstract

Objective: **The aim of the present investigation is to determine if the tissue reaction to the *Riccinus communis* (mamona) polymer has significant statistical difference compared to the tissue reaction provoked by the titanium implant.**

Methods: **Thirty two *Cavia porcellus* were divided into four groups containing eight animals each one. We implanted the two types of materials in the retroperitoneal space of all the animals. They were sacrificed at 7, 20, 30 and 40 days after surgery and the samples were submitted to histological study.**

Results: **The quantitative analysis did not show difference between the tissue reaction of the two materials (*P*>0.05). The analysis of the qualitative variable also did not show difference between the tissue reaction of the materials (*P*>0.05).**

Conclusion: **Macroscopic and microscopic results showed that the castor oil polymer implant has no significant statistical difference compared to the titanium implant tissue reaction.**

Descriptors: **Prosthesis implantation. Heart, artificial. Ricinus. Implants, experimental. Guinea pigs.**

Resumo

Objetivo: **Determinar se a reação tecidual do implante retroperitoneal do polímero de óleo de mamona (Pm) é significativa ou não por meio de análise histopatológica, tendo como controle o implante de titânio (Ti).**

Métodos: **Estudo experimental, intervencionista e randomizado com 32 cobaias. Os animais foram divididos em quatro grupos iguais e eutanasiados com 7, 20, 30 e 40 dias após**

1. Denton Cooley-CEVITA Institute, Post-Doctorate in Medicine from Universidade Federal do Paraná, Director of the Heart Institute of Curitiba - Hospital Vita, Curitiba, PR, Brazil. Realization of experimental surgeries; writing of the manuscript.
2. Denton Cooley-CEVITA Institute, Academic Head of the Denton Cooley Research Institute, Graduating in medicine from Faculdade Evangélica do Paraná, Curitiba, PR, Brazil. Review of literature; realization of experimental surgeries; writing of the manuscript.
3. Denton Cooley-CEVITA Institute; Scientific Initiation Scholarship PIBIC / CNPp 2011-2012; Graduating in medicine from Faculdade Evangélica do Paraná, Curitiba, PR, Brazil. Review of literature; realization of experimental surgeries; writing of the manuscript.
4. Faculdade Evangélica do Paraná; Professor and Pathologist, Curitiba, PR, Brazil. Reading and Report of the blades of pathological analysis.
5. Pontifícia Universidade Católica do Paraná - PUCPR; Doctorate in Health Sciences PUCPR, Curitiba, PR, Brazil. Statistical analysis.
6. Denton Cooley-CEVITA Institute; Resident in Cardiovascular Surgery at the Texas Heart Institute, Houston, Texas, USA. Realization of experimental surgeries.

Work performed at the Denton Cooley - CEVITA Institute, InCor, Curitiba, PR, Brazil.

Correspondence address: Luiz Fernando Kubrusly
Rua Alferes Ângelo Sampaio, 1896 – Batel – Curitiba, PR, Brazil – Zip code: 80420-160
E-mail: kubrusly@incorcuritiba.com.br

Article received on May 8th, 2012
Article approved on August 23th, 2012

Abbreviations, acronyms and symbols	
CO2	Carbon dioxide
COBEA	Colégio Brasileiro de Experimentação Animal
CAD	Circulatory assist devices
HE	Hematoxylin-eosin
CHF	Congestive heart failure
Pc	Polymer castor
PVPI	Polyvinylpyrrolidone iodine
Ti	Titanium

o ato cirúrgico. Foram confeccionadas lâminas em hematoxilina-eosina e em tricrômio de Masson. Na comparação dos tipos de material em relação a variáveis quantitativas, foi considerado o teste não-paramétrico de Wilcoxon. Em relação a essas variáveis, os grupos definidos pelo dia do sacrifício foram comparados usando-se o teste não-paramétrico de Kruskal-Wallis. Os resultados obtidos no estudo da fibrose foram expressos por frequências e percentuais. Para a comparação entre os grupos definidos pelo dia do sacrifício, em relação a variáveis qualitativas dicotômicas da fibrose, foi considerado o teste exato de Fisher. Para avaliar a diferença entre os materiais titânio e polímero em cada grupo, ainda em se tratando da fibrose, foi considerado o teste binomial. Valores de *P*<0,05 indicaram significância estatística.

***Resultados:* A análise das variáveis quantitativas não demonstrou diferença nas reações teciduais entre os materiais (*P*>0,05). A análise da variável qualitativa também não demonstrou diferença entre as reações teciduais dos materiais (*P*>0,05).**

***Conclusão:* Não foi encontrada significância estatística entre a reação tecidual do Pm e do Ti.**

***Descritores:* Implante de prótese. Coração artificial. Ricinus. Cobaias. Implantes experimentais.**

INTRODUCTION

Cardiovascular diseases are the leading cause of death worldwide and, for the first time in history, that leadership is independent of socioeconomic status of countries. Considering the aging population worldwide, despite the epidemiological and medical practices, it is expected that this prevalence can be maintained or even increase in the coming decades [1].

Congestive heart failure (CHF) is among those diseases and competes today with a high prevalence in several countries. In the United States of America, an estimated 400 000 new cases per year [2].

Since the pioneering work of De Bakey in 1966 [3], with the placement of the first ventricular assist device, and Cooley in 1969 [4], with the implantation of the first totally artificial heart in a patient with cardiogenic shock, cardiovascular medicine has been trying to develop a technology capable of keeping these serious patients alive. The circulatory assist devices (CADs), recently became a key part of the therapeutic armamentarium in the treatment of cardiogenic shock and in maintaining circulatory support in patients with terminal heart failure [5,6]. The use of these devices has been indicated as a bridge to heart transplantation, as support for the recovery of the heart in acute myocardial infarction and post-cardiac surgery [7,8]. Another indication restricted to centers much more research in this area is the destination therapy for treatment of CHF terminal. Some studies have shown mortality at 1 year, similar among heart transplant and destination therapy. [9].

Since 1997, we began developing a CAD that was accessible to public service in our country. We perform tests "*in vitro*" [2] and idealized device constructed from titanium, and the vast majority of the equipment available in the world. Tests "*in vivo*" experiments were carried out on sheep and proved the effectiveness of the device [2]. Within our main objective, which is the development of national equipment, adapted to the resources of our country, we are in the process of replacing high-cost mechanical parts for substitutes acquired nationally and therefore at lower costs.

Castor oil is a vegetable oil extracted from the seeds of the plant *Ricinus communis*, which is found in tropical and subtropical regions. It viscous liquid obtained by pressing (hot or cold) of seeds or by solvent extraction [10]. Studies of the use of castor oil and derivatives for the synthesis of polyurethanes began in late 1940 with the preparation of polyurethane films for coating surface [11].

The first reports on the use of polyurethanes in medical applications date back to 1959 when Mandarino & Salvatore implanted a rigid foam polyurethane for fixation of bone *in situ*.

The polyurethanes of castor oil can be obtained with different characteristics, since the most flexible, as elastomers, to the most rigid, like the bone cements. Several biocompatibility studies were conducted mainly in

bone: in orthodontic implants, bone fixation plates, sealants [12] in cranioplasties in orthopedic prostheses and orbital reconstruction [13].

The objective of this study is to evaluate this type of polyurethane castor, to obtain histological data sufficient to prove that the low inflammatory reaction in the retroperitoneal space of guinea pigs compared to that of titanium.

METHODS

Interventional and randomized experimental study, developed by the Denton Cooley Institute in the Laboratory of Histology and Cell Biology, in the Animal Clinical and Surgical Experimentation Laboratory of Faculdade Evangélica do Paraná.

Ethical aspects

This manuscript was submitted to the Ethics Committee in Research of the Evangelical Beneficent Society of Curitiba and approved with number 4277/11.

This was followed by the Act 6638 of May 8, 1979, Standards for the Practice of Scientific-Didactic Animal Vivisection.

The standards established in the "Guide for the Care and Use of Laboratory Animals" (Institute of Laboratory Animal Resources, National Academy of Sciences, Washington, DC, 1996) and the precepts of the Brazilian College of Animal Experimentation (COBEA) were also obeyed.

Sample

A total of 32 guinea pigs (*Cavia porcellus*), Rodentia, Mammalia, males, weighing between 250 and 300 grams (mean: 289.15 ± 17.47), from the Institute of Technology of Paraná, aged 4 and 6 months Life, previously healthy, created and maintained under similar environmental conditions and food were utilized.

The animals were randomly divided into four groups (A, B, C, D) of equal size. They were euthanized in a CO_2 gas chamber, four animals per time at 7 (group A), 20 (group B), 30 (group C) and 40 (group D) days after implant surgeries [14].

Setting experimentation

The guinea pigs were housed according to the Manual of Technical Standards for Animal Experimentation Animal Facility of the Department of Microbiology, Institute of Biomedical Sciences, University of São Paulo. [15] The laboratory used was the one of Faculdade Evangélica do Paraná, where the light / dark cycle and humidity are the general environment. The temperature was kept constant (24°C) and their cages were placed all at the same height from the ground. The animals received filtered water and standard commercial diet *ad libitum* until 4 hours before euthanasia. The analgesia protocol followed dose Tramadol 1 mg / kg of 12-24 hours duration [15]. The animals were previously acclimated for a period of 7 days prior to the realization of the experiments. Surgical procedures were performed under refrigeration, sterile technique and material, in the Clinical and Experimental Surgery Laboratory of the Faculdade Evangélica do Paraná (Figure 1).

Anesthesia

The animals were anesthetized as recommended by Radde et al. [16], using ketamine and xylazine (87/13 mg / kg, respectively), both applied intraperitoneally.

Description of surgery

Once anesthetized, the animal was positioned prone and shaving was done bilaterally with scissors along the back. Subsequently, it was performed antisepsis of the surgical field with polyvinylpyrrolidone iodine (PVP).

It was performed local anesthesia with lidocaine 2% diluted in physiological saline solution. The procedure was then an incision of 2 cm in length at 2 cm of the left vertebral axis in the region between the last rib and iliac crest. The procedure crossed the epithelium, the subcutaneous tissue, fascia and hit the muscular layer. The muscle was carefully opened and hit the virtual retroperitoneal space where the titanium (Ti) disc was implanted. The deep and superficial incision planes were sutured with 3-0 nylon line [17], with continuous simple stitches. On the right side it was proceeded in the same way, but the implant was polymer castor (Pc).

Collecting material for histopathologic study

The surgical device was removed in monobloc and immediately immersed in neutral buffered formalin 10% and remained in fixative for 72 hours at room temperature. After fixation, the discs of Ti and Pc were removed by lateral incision and then the pieces were washed in water for 24 hours, processed routinely and embedded in paraffin. The material received cuts of 6 micrometers and was stained by using hematoxylin-eosin (HE) for the cellular elements and capillaries, and by the technique of Masson trichrome with Blue Nile for collagen fibrosis. Analysis was performed by means of optical microscope Olympus® brand, model DX 50.

Microscopic examination was performed in order to assess the inflammatory process of each material, i.e., congestion and the formation of granulation tissue peri-implant. For this, it has been found quantitatively the number of inflammatory cells in each blade of each group. The cells analyzed were histiocytes, neutrophils, lymphocytes and giant cells. The histiocyte considered in

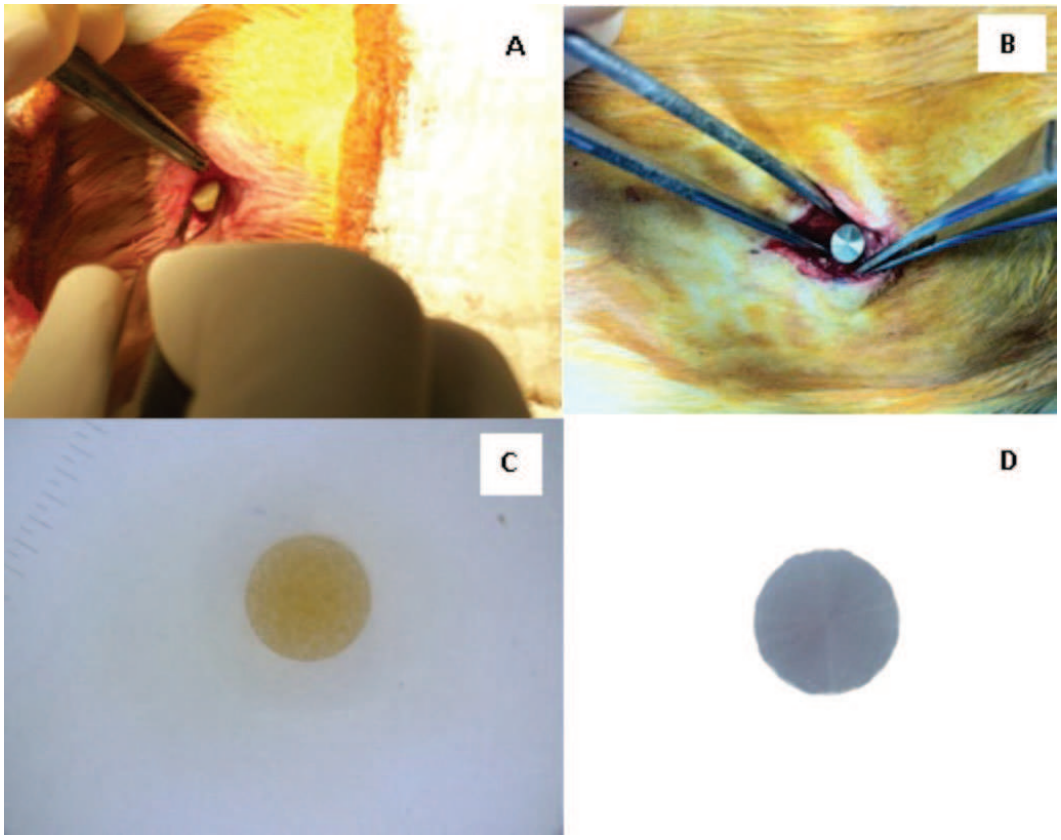

Fig. 1 - Implants Pc (A) and Ti (B) in anatomical site. In C, you can see the implant Pc; in D, we have the implant Ti

this study as a histopathologic type of macrophage of reticuloendothelial origin, which is normally stationary and inactive, but could become active if stimulated, a neutrophil, a polynuclear leukocyte of neutrophil granules, the lymphocyte, a type of white blood cell having between 10-12 micromeres in diameter, a round nucleus with condensed chromatin and scarce cytoplasm a bit basophilic; the giant cell, as being that formed by the union of several distinct cells.

Regarding the presence of fibrosis, this was classified as mild, moderate or severe.

For microscopic examination it was used 10X eyepiece, focusable and objective of 40X. For reading, the cell types were counted in 10 microscopic fields with the abovementioned increase in areas altered by inflammatory foreign body.

Preparation and origin of implants

The Ti was the control material, while Pc was the material put to test. The alloy of Ti was obtained from commercial establishment, cylindrical rods with 5 mm diameter characterized as grade 2; the bar chemical composition was 99.7% Ti, 0.009% C, 0.095% Fe, 0.0003% H, 0.0038% N and 0.152% O_2; regarding the mechanical properties, the bar presented% Elongation (N) L = 32,% RED. IN AREA L = 52, L = 78.8 ksi UTS and YS ksi (0.2%) L = 57.

The Pc was obtained in liquid form by laboratory specializing in polymers used in the medical field (Poliquil - Araraquara, SP, Brazil). The process of making the implants castor starts from equal parts of a polyol and an ampoule bulb vegetable polyurethane resin hardener which are mixed with glass rod in a beaker for 3 minutes until complete homogenization. There was no addition of calcium carbonate. The homogenate obtained was placed in two insulin syringes. After polymerization completed, the syringes were sectioned with a scalpel blade in transverse sections of 3 mm thickness, then withdrawing the plastic of the syringe barrel [18]. Thus we obtained the discs of 3 mm thick and 5 mm in diameter to be used in retroperitoneal implantation in mice. The antisepsis of the disks was done

by submerging them in alcohol 70° for 15 minutes. The process of making the Ti implants was performed in a specialized factory (Neodent - Curitiba, PR, Brazil). The bar of Ti was arrested plate lathe (20A-Tormax ROMI) and sectioned along with cutting fluid (Quimatic oil), then the disks obtained were made square to be free of spikes or irregularities resulting from the first process. Ti implants had the same dimensions of the castor implants and were also sterilized in alcohol 70 °.

Statistical analysis

Comparing the types of material with respect to quantitative variables was considered the nonparametric Wilcoxon [19]. In terms of these variables, the groups defined by the day of sacrifice were compared using the nonparametric Kruskal-Wallis test [19]. The results obtained in the study of fibrosis and frequencies were expressed as percentages. For comparison between the groups defined by the day of sacrifice, for dichotomous qualitative variables fibrosis, it was considered the Fisher exact test [19]. To evaluate the difference between titanium and polymer materials in each group, although in the case of fibrosis, it was considered the binomial test [19]. P values <0.05 were considered statistically significant. Data were analyzed with Statistica v.8.0 program.

RESULTS

There were no complications related to the surgical site, such as dehiscence or infection.

Analysis of quantitative variables

Initially considering each of the groups A, B, C and D for each of the variables relating to the number of lymphocytes, histiocytes, neutrophils and giant cells, we tested the null hypothesis that the results of Pc are equal to Ti, versus the alternative hypothesis of different results.

In group A, by quantifying lymphocytes (Pc: mean 35, median 34; Ti: mean 34.1, median 34), histiocytes (Pc: mean 279, median 270; Ti: mean 283.9, median 298), neutrophils (Pc: mean 0.4, median 0, Ti: mean 0.9, median 0) and giant cells (Pc: mean 7.1, median 6; Ti: mean 6, median 6), no difference was found between The two materials (P> 0.05).

In group B, by quantifying lymphocytes (Pc: mean 32.4, median: 32.5, Ti: mean 46.1, median 40.5), histiocytes (Pc: mean 183.6, median 205; Ti: mean: 182.8, median 147), neutrophils (Pc: mean 11.5, median 3; Ti: mean 5.8, median 3) and giant cells (Pc: mean 5.3, median 3.5, Ti: mean 1 , 6, median 1), no difference was found between the two materials (P> 0.05).

In group C, by quantifying lymphocytes (Pc: mean 14.4, median 15; Ti: mean 20.1, median 16), histiocytes (Pc: mean 275.6, median: 278; Ti: mean 295.7, median 278), neutrophils (Pc: mean 0, median 0, Ti: mean 0, median 0) and giant cells (Pc: mean 4.3, median 3; Ti: mean 9.9, median 9), no difference was found between the two materials (P> 0.05).

In group D, by quantifying lymphocytes (Pc: mean 3, median 3; Ti: mean 8.7, median 8), histiocytes (Pc: mean 120.1, median 115; Ti: mean 157.1, median 176), neutrophils (Pc: mean 0, median 0, Ti: mean 0, median 0) and giant cells (Pc: mean 4.3, median 5; Ti: mean 5.3, median 5), no difference was found between The two materials (P> 0.05). Then, for each type of material tested the null hypothesis that results in the four groups are equal, versus the alternative hypothesis that at least one of the groups have different results than others. Where there rejection of the null hypothesis (P <0.05), groups were compared two by two.

When comparing the four groups of Pc each other, it was observed that there was a tendency of reducing the number of inflammatory cells over time post-operatively (P <0.05). In making the same analysis for the 4 groups of Ti, trend was also observed for the reduction of inflammatory cells over time (P <0.05) (Figures 2 to 5).

The peri-implant fibrosis tended to be equally sharp in both types of implanted material with the passage of time. In groups A and C, when comparing the two types of materials implanted P was not highly significant (P = 0.5). In the other groups, to make the same analysis, we found that P was not highly significant (P = 1).

Study of the qualitative variable

Regarding the correlation study the intensity of the peri-implant fibrosis in group A, it was found that five cases (62.5%) of Pc presented not accentuated grade, while the Ti showed two cases (25%); in regarding the high level of fibrosis in group B, there were three cases (37.5%) of Pc and six cases (75%) P value Ti (Ti x Pc) in group A was 0.500, i.e., not significant, since P> 0.05.

Regarding the study in the group B, it was observed that three patients (37.5%) of Pc showed no accentuated degree, while the Ti showed two cases (25%); regarding the high level of fibrosis in that group it had five cases (62.5%) of Pc and six cases (75%) P value Ti (Ti x Pc) in Group B was 1, i.e., not significant, since P> 0.05.

Regarding the study in the group C, there was a case (12.5%) of Pc that showed no accentuated degree, while the Ti showed two cases (25%); regarding the high level of fibrosis in that group there were seven cases (87.5%) of Pc and six cases (75%) P value Ti (Ti x Pc) in group C was 0.500, i.e., not significant, since P> 0, 05.

Regarding the study in the group D, it was found that three cases (37.5%) of Pc and also three cases (37.5%) of Ti showed no accentuated degree, regarding the high level of fibrosis in that group there were five cases (62.5%) of Pc and number of cases of the same P value Ti (Ti x Pm) in group D 1, i.e., not significant, since P> 0.05 (Figure 6).

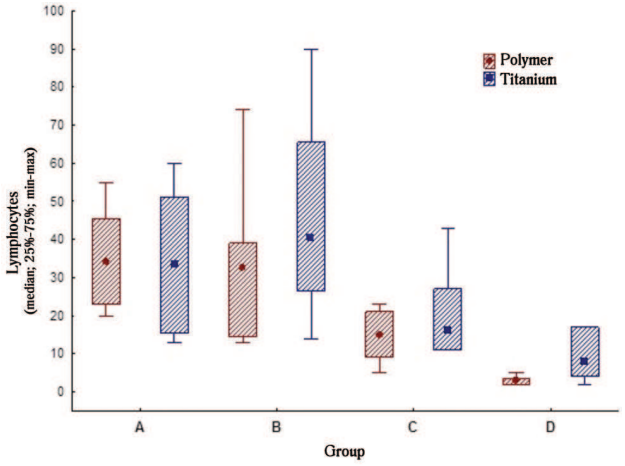

Fig. 2 - Quantitative analysis of lymphocytes according to defined group

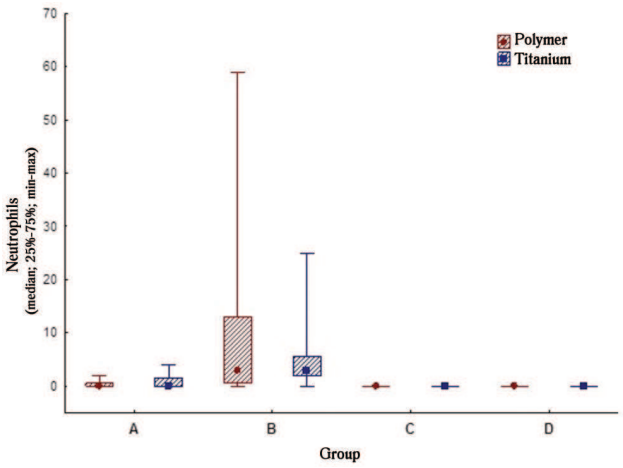

Fig. 4 - Quantitative analysis of neutrophils according to defined group

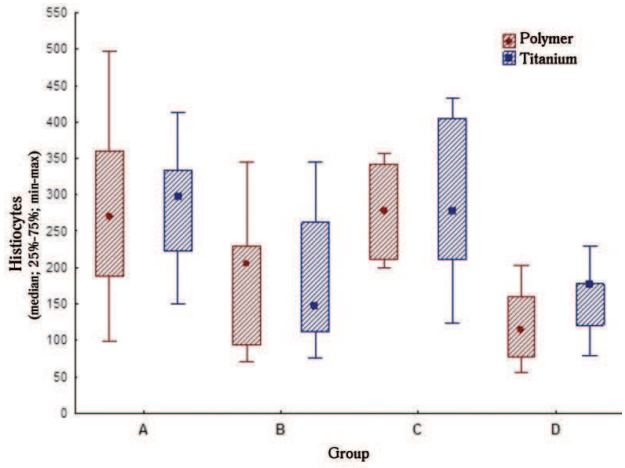

Fig. 3 - Quantitative analysis of histiocytes according to defined group

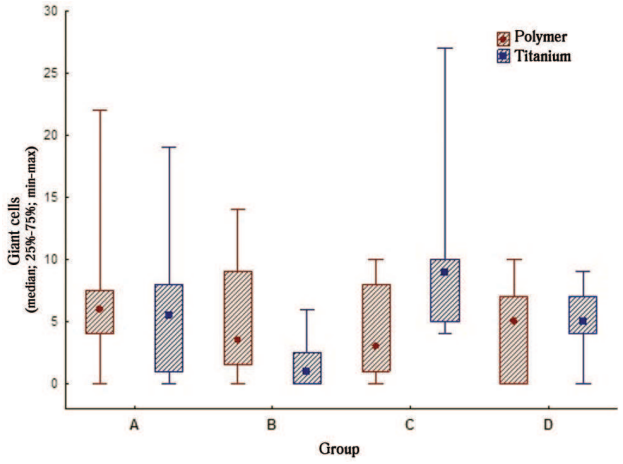

Fig. 5 - Quantitative analysis of giant cells according to defined group

DISCUSSION

It was chosen the *Cavia porcellus* by experience of the research group, as its size and docile nature facilitated the manipulation of the retroperitoneum. The serosa of smaller animals, such as rats and *Wistar* mice is more labile, impeding dilatation of the retroperitoneal space, so complications including migration of the implant and rupture of the peritoneal membrane could be more frequent in these smaller animals.

We used a guinea pig for every two implants (Pc and Ti). It was decreased, thus, the number of animals in the experiment to deploy a different material in each hemisphere of the same guinea pig. The implant site was the retroperitoneum, for it is a membrane similar to the pericardial and pleural membranes of the thoracic cavity, site characteristic of implantable circulatory assist devices.

Low cost materials, acceptable biocompatibility characteristics and abundant in nature would be ideal to replace other materials that already exist in practice, but that have high costs and are difficult to obtain.

The favorable characteristics found in Pc were first cited by the authors such as Ohara et al. [20] Carvalho et al. [21] Ignacio et al. [22] and Silva [23], paving the way for the use of this polymer in orthopedics, orthodontics, surgery and oral maxillofacial neurosurgery. Furthermore, the system of

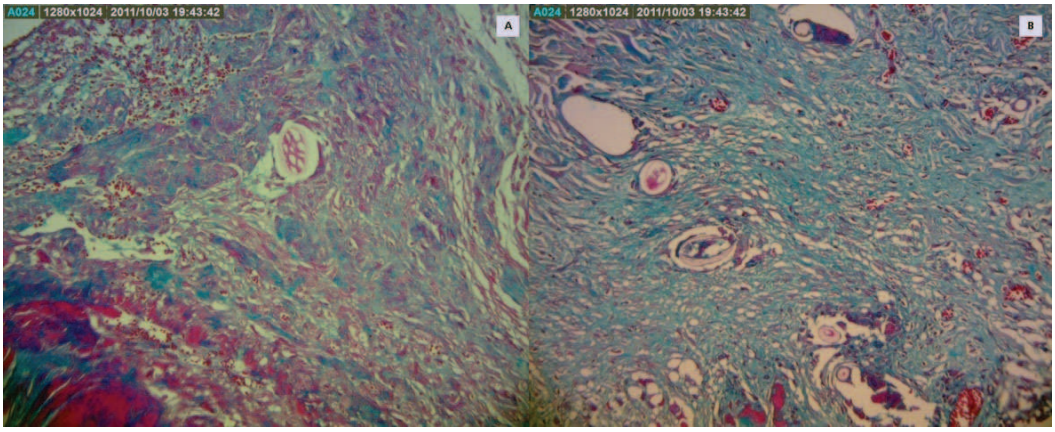

Fig. 6 - Blades of group D of Ti (A) and Pc (B) in the Masson's Trichrome staining, indicating moderate fibrosis in both

obtaining Pc is very attractive because it eliminates the presence of catalysts; it has simple processability and flexibility in the formulation, thereby adding other components without interfering with the reaction. There is versatility of "cure" temperature with a maximum exothermic peak of 45 degrees centigrade, with no residual free monomer production post-reaction, which was not desirable in a circulatory assist device, common among polymers and encouraged researchers to use titanium therefore. Dias et al. [24] conducted a study using four capuchin monkeys, placing an implant of a bone defect in Pc, previously performed in the nasal dorsum of these animals; later, histological analysis did not reveal the presence of foreign body granuloma or phagocytic cells. Although our study did not perform analysis on bone tissue, there was also the presence of foreign body granuloma in histological analysis. Another study of Mastrantonio & Ramalho [18] evaluated the response of connective tissue of mice to Pc for 60 days, and again the result was favorable biocompatibility.

The Ti is considered inert and authors like Bothe et al. [25] have amply demonstrated their applicability in metal alloys in the medical field since the mid-twentieth century. Ti alloys are widely used as part replacement of bones in the human body implantable materials such as screws and plates, which today appear including reconstructive surgery. Likewise, the Pm is increasing the scope of its area of use.

It was observed in this study that the predominant type of inflammation, in both studied materials (Pc and Ti), was the chronic inflammation, i.e., predominance of mononuclear cells and that, regardless of the period analyzed, the granulation tissue was predominant in non accentuated.

The initial period of 7 days is directly related to suturing performed during surgery. Siqueira & Dantas [26] described as the period of deposition of collagen and hyaluronic acid, which compounds are produced in an attempt to rebuild the damaged tissues. In the present study, the first 7 days, inflammation was non accentuated, beyond that, there was no statistically significant difference in the degree of granulation tissue in both groups.

The largest amount of fibrosis found in the last two groups, i.e., 30 and 40 days postoperatively, was discordant results of Costa et al. [27] found that the formation of a dense fibrous tissue involving the Pc. In this study, for both materials, the adjacent tissue showed histological characteristics of normal, and show a tendency to reduced tissue reaction with the progression of the time of deployment.

Another situation was that there was gross and microscopic structural degradation of the polymer when subjected to temperatures from the animal. This can be confirmed by the thesis that the polyurethanes showed thermal stability up to 210 ° C, demonstrating that, at room temperature, these polymers have no possibility to undergo thermal decomposition [28].

In addition to the stability at high temperatures, Pc is a Brazilian technology and represents the possibility of an implantable device with less weight for the patient. The device in our study, K-pump, made of steel, has its weight of 194 g. With the same dimensions, built in titanium, the projected weight is between 85-95 g. With the polymer castor, the weight will be around 50 g, weight below the average of major totally implantable devices currently available and suitable for pediatric patients and small adults.

CONCLUSION

The tissue reaction induced by the two materials is very similar. There was no statistically significant difference between the tissue reaction caused by implantation of Pc and tissue reaction caused by Ti implantation in guinea pigs.

ACKNOWLEDGEMENTS

Denton Cooley Research Institute, for supporting and encouraging us in this work.

Vita Studies Center, which has provided conditions for this study.

The company Poliquil (Araraquara, SP, Brazil), in particular Messrs. Antonio Carlos Rossi and Alexandre Guillen, who helped provide the polymer castor.

The company Neodent (Curitiba, Brazil), in particular to Mr. Adailton Becker, who helped us with the handling and cutting of titanium parts.

Faculdade Evangélica do Paraná, for the solicitude and support at all stages of this research.

REFERENCES

1. Roscani MG, Matsubara LS, Matsubara BB. Insuficiência cardíaca com fração de ejeção normal. Arq Bras Cardiol. 2010;94(5):694-702.

2. Kubrusly LF, Martins AF, Madeira J, Savytzky S, Wollman D, Melhem A, et al. Dispositivo de assistência circulatória mecânica intraventricular de fluxo axial: estudo in vitro. Rev Bras Cir Cardiovasc. 2000;15(2):169-72.

3. Tayama E, Olsen DB, Ohashi Y, Benkowski R, Morley D, Noon GP, et al. The DeBakey ventricular assist device: current status in 1997. Artif Organs. 1999;23(12):1113-6.

4. Gray NA Jr, Selzman CH. Current status of the total artificial heart. Am Heart J. 2006;152(1):4-10.

5. Dinkhuysen JJ, Andrade A, Contreras C, Paulista PP, LEME J, Manrique R. Estudo experimental da aplicação do ventrículo artificial eletromecânico pulsátil implantável. Rev Bras Cir Cardiovasc. 2011;26(1):76-85.

6. Moreira LFP; Benício A. Assistência circulatória mecânica: uma grande lacuna na cirurgia cardíaca brasileira. Rev Bras Cir Cardiovasc. 2010;25(4):X-XII.

7. Portner PM, Oyer PE, Pennington DG, Baumgartner WA, Griffith BP, Frist WR, et al. Implantable electrical left ventricular assist systems: bridge to transplantation and the future. Ann Thorac Surg. 1989;47(1):142-50.

8. Shreenivas SS, Rame JE, Jessup M. Mechanical circulatory support as a bridge to transplant or for destination therapy. Curr Heart Fail Rep. 2010;7(4):159-66.

9. Frazier OH, Rose EA, Macmanus Q. Multicenter clinical evaluation of the HeartMate 1000 IP left ventricular assist device. Ann Thorac Surg. 1992;53(6):1080-90.

10. Chierice GO, Claro Neto S. Aplicação industrial do óleo. In: Azevedo DMP, Lima EF, eds. O agronegócio da mamona no Brasil. Brasília:Embrapa;2001.

11. Saunders JH, Frish KC. Polyurethanes: chemistry and technology. New York:John Wiley;1962. 368p.

12. Fedak PW, Kolb E, Borsato G, Frohlich DE, Kasatkin A, Narine K, et al. Kryptonite bone cement prevents pathologic sternal displacement. Ann Thorac Surg. 2010;90(3):979-85.

13. Gurgel JD, Alves Filho L, Farias VLD, Portugal AM, Sarmento Júnior KM. Ricinus communis membrane for orbital reconstruction. Braz J Otorhinolaryngol. 2011;77(2):268.

14. Brito MKM, Schellini SA, Padovani CR, Pellizzon CH, Neto CGT. Inclusões de quitosana no subcutâneo de rato: avaliação clínica, histológica e morfométrica. Anais Bras Derm. 2009;84(1):35-40.

15. Taborda PC, Carlos T. Manual de normas técnicas. Biotério de experimentação animal. São Paulo: Departamento de Microbiologia Instituto de Ciências Biomédicas – USP; 2004.

16. Radde GR, Hinson A, Crenshaw D, Toth LA. Evaluation of anaesthetic regimens in guineapigs. Lab Anim. 1996;30(3):220-7.

17. Ribeiro CMB, Silva Júnior VA, Silva Neto JC, Vasconcelos BCE. Estudo clínico e histopatológico da reação tecidual às suturas interna e externa dos fios monofilamentares de nylon e poliglecaprone 25 em ratos. Acta Cir Bras. 2005;20(4):284-91.

18. Mastrantonio SS, Ramalho LTO. Mouse connective tissue reaction to poliurethane derived from castor oil. Rev Odontol UNESP. 2003;32(1):31-7.

19. Siegel S, Castellan JR, John N. Estatística não-paramétrica para ciências do comportamento. 2ª ed. Porto Alegre: Artmed Editora; 2006.

20. Ohara GH, Kojima KE, Rossi JC, Telles M, Soares TVC, Salomão C, et al. Estudo experimental da biocompatibilidade do polímero poliuretano da mamona implantada intra-óssea e intra-articular em coelhos. Acta Ortoped Bras. 1995;3(2):62-8.

21. Carvalho TL, Araújo CA, Teófilo JM, Brentegani LG. Histologic and histometric evaluation of rat alveolar wound healing around polyurethane resin implants. Int J Oral Maxillofac Surg. 1997;26(2):149-52.

22. Ignácio H, Mazzer N, Barbieri CH, Chierici G. Uso da poliuretana derivada do óleo de mamona para preencher defeitos ósseos diafisários segmentares do rádio. Estudo experimental em coelhos. Rev Bras Ortop. 1997;32(10):815-21.

23. Silva MJA. Estudo radiográfico das imagens convencionais e digitalizadas do comportamento do tecido ósseo frente ao implante do polímero de mamona em coelhos [Dissertação de mestrado]. Bauru:Faculdade de Odontologia de Bauru – USP;1999. 135p.

24. Dias PCJ, Granato L, Pretel H. Avaliação histológica da biocompatibilidade do polímero da mamona no dorso nasal de macacos-pregos. Cebus apella. Braz J Otorhinolaryngol. 2009;75(3):350-5.

25. Bothe RT, Beaton LE, Davenport HA. Reaction of bone to multiple metallic implants. Surg Gynecol Obstetr. 1940;71:598-602.

26. Siqueira Jr JF, Dantas CJS. Inflamação: aspectos biodinâmicos das respostas inflamatória e imunológica. Rio de Janeiro:Pedro Primeiro;1996.

27. Costa CAS, Marcantonio RAC, Hebling J, Teixeira HM, Kuramae M. Biocompatibilidade do polímero de poliuretana vegetal derivada do óleo de mamona em estudo comparativo com cimento de óxido de zinco e eugenol: avaliação histopatológica de implantes subcutâneos de ratos. Odonto 2000. 1997;1(1):44-8.

28. Pereira PHL. Estudo das propriedades físico-químicas da poliuretana derivada do óleo de mamona com potencial aplicação na área médica [Dissertação de mestrado]. São Carlos:Universidade de São Paulo, Instituto de Química de São Carlos;2010 [Acesso 2012-06-25]. Disponível em: http://www.teses.usp.br/teses/disponiveis/75/75132/tde-26072010-141545/.