Comparison of the occurrence of thromboembolic and bleeding complications in patients with mechanical heart valve prosthesis with one and two leaflets in the mitral position

Comparação da ocorrência de complicações tromboembólicas e hemorrágicas em pacientes portadores de prótese valvares cardíacas mecânicas com um e dois folhetos na posição mitral

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Abstract

Introduction: Patients with mechanical heart valve prostheses must continuously be treated with oral anticoagulants to prevent thromboembolic events related to prosthesis. These patients should be continually evaluated for the control of oral anticoagulation.

Objective: To compare the occurrence of thromboembolic and hemorrhagic complications in patients with mechanical heart valve prosthesis with one (mono) and two (bi) leaflets in the mitral position in anticoagulant therapy.

Methods: We studied the 10-year interval, 117 patients with prosthesis in the mitral position, 48 with prosthetic single leaflet and 69 with two leaflets. We evaluated the occurrence of thromboembolic and hemorrhagic major and minor degree under gravity. The results are presented in an actuarial study and the frequency of occurrence of linear events.

Results: The actuarial survival curves showed that over time, patients with prosthetic heart valve with one leaflet were less free of thromboembolic complications than patients with two leaflet prosthetic valve, while the latter (two leaflet) were less free of hemorrhagic accidents. The linearized frequency of occurrence of thromboembolism were higher in patients with mono leaflet prosthesis. Bleeding rates were higher for patients with bi leaflet prosthetic valve.

Conclusion: Patients with mono leaflet prosthetic heart valve showed that they are more prone to the occurrence of serious thromboembolic events compared to those with bi leaflet prosthetic valve. Patients with bi leaflet prosthetic valve had more bleeding than patients with mono leaflet prosthetic valve, however this difference was restricted to the bleeding of minor nature.

Descriptors: Anticoagulants. Embolism and Thrombosis. Hemorrhage. Heart Valve Prosthesis.

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INTRODUCTION

The implantation of mechanical heart valve prosthesis requires the need for continuous use of oral anticoagulants for its potential thrombogenicity and thromboembolism [1].

An individualized approach in the monitoring of patients with mechanical heart valve prosthesis receiving oral anticoagulation is essential to obtain satisfactory results in the control of oral anticoagulation. Besides the type of prosthesis used, the risks inherent in each patient to thromboembolism, bleeding, and the anatomical position of the prosthesis are also important [2].

The mechanical heart valve prostheses have been produced since the 1950s and are primarily made of metal and carbon alloy after being classified as prosthetic cage-ball-type, single disc (or mono-leaflet or uni-leaflet) and double disc (or bi-leaflet). Those with higher thrombogenic potential are the cage-ball and those with lower thrombogenicity are the bi-leaflet, and the bi-leaflet valve prostheses are in position between the previous two. However, in patients with adequate anticoagulation, the incidence of thrombosis is similar for the three types of mechanical [3] prostheses.

For Lavitola et al. [4] in certain situations, in patients with mitral bioprosthesis in the presence of atrial fibrillation, where is commonly indicated prophylaxis with oral anticoagulants, the replacement of the anticoagulant by aspirin could be considered. However, for mechanical prostheses, continuous oral administration of antivitamin K would always be indispensable, with or without concomitant atrial fibrillation. Bussey [5] states that many studies do not consider some factors that influence the thrombogenicity, among them, the prosthesis structure (type).

Currently, the use of mechanical heart valve prostheses is performed almost in its entirety with bileaflet prostheses. The mono-leaflet prostheses were out of use in cardiac surgery for valve performance problems and other complications in some models more than other types of prostheses. In 1986, for example, the convexo-concave Bjork-Shiley
prosthesis stopped being used due to reports of the fracture ring, and embolization resulting in displacement of the plate [3].

For many years, the mechanical mono-leaflet prosthesis has not been used in our cardiovascular surgery service, which made gradually decrease the number of patients with this type of prosthesis with respect to bi-leaflet prostheses. However, many of the patients followed for control of anticoagulation carries prosthesis with single disc and will continue this behavior permanently.

Several studies have assessed the occurrence of thromboembolic and bleeding complications in patients with mechanical mono-leaflet heart valve prostheses [6-9] and double bi-leaflet [10,11], however, without comparing the two types of prosthesis. Then, we perform a particular study comparing patients with mono- and bi-leaflet prosthesis in the mitral position, given that patients have no cage-ball in this position. We question whether a prosthesis of different model, supposedly developed with most advanced technology could indeed cause less thromboembolic and bleeding complications than other older models.

METHODS

Outpatient data and hospital records of patients with mechanical heart valve prostheses in the mitral position were obtained, followed-up in the Outpatient Anticoagulation Control Unit, Clinics Hospital, Faculty of Medicine of Botucatu, UNESP. Due to the fall into disuse in our service, the mono-leaflet mechanical prostheses (or uni-leaflet or single disc) in 1995, the interval between January 1, 1993 to December 31 (ten years) 2002 was established because it is a period in which the number of patients with the two types of prostheses, with regular visits at the clinic, allows a better comparison of the data. After the above mentioned period, only came into monitoring patients with double leaflet prostheses (or bi-leaflet), which limited the entry of new patients and the expansion of the observation period. All data were collected and organized by the same researcher.

This study was approved by the Research Ethics Committee of the Faculty of Medicine of Botucatu - São Paulo State University - UNESP, under CEP registry OF605/2006. The patients signed a written informed consent for the use of their records and service forms before the beginning of data collection, as required by the Ethics and Research Committee.

Patients

Number of Patients

In this study, 117 patients with prosthesis in the mitral position, of which 48 prostheses were mono-leaflet and 69 bi-leaflet (Chart 1) were included. During the study period, patients made use of two types of anticoagulants: warfarin and phenprocoumon.

![Chart 1. Models of mechanical heart valve prostheses implanted.](chart1)

| Model          | Mitral |
|----------------|--------|
| Bicarbon       | 46     |
| St Jude Medical| 23     |
| Omnicarbon     | 17     |
| Omniscience    | 15     |
| Sorin-mono     | 13     |
| Lilliehi-Kaster| 1      |
| Edwards        | 1      |
| Hall-Kaster    | 1      |
| TOTAL          | 117    |

Age and gender

As the study performed follow-up of patients over a period of time, it was considered the standard for each patient his age at the time of implant surgery prosthesis. The mean age of patients was 40.97 years.

84 women and 33 men participated. Mean age of 41.12 years for women and 40.58 years for men.

Patients excluded from the study

Patients in whom it has not been possible to obtain sufficient or reliable data for the study were excluded from the study.

The outpatient anticoagulation control

During the consultations, the guidance on care and importance of anticoagulation are strengthened, trying to leave no doubt in understanding the dose of anticoagulant to be used.

Patients should be cautioned about signs of bleeding, and if it occurs, they should seek the Emergency Room of the Clinics Hospital immediately. Patients with significant complaints or signs related to anticoagulation, as well as greatly increased INR (even without bleeding), hospitalized in Cardiovascular Surgery Nursery. When hospitalization is necessary, but there are complaints of minor bleeding or other less significant changes, a return is scheduled as soon as possible, as the case requires. When the patient’s INR is well controlled, a monthly return is scheduled. Deviations of INR require returns in smaller spaces of time. In general, patients who have about four returns with satisfactory INR (four months), will have returns every two months. Patients who, for some reason, come in search of care are met, even if they are not scheduled for that day.

We considered the ranges of INR desired at each visit for patients with prosthetic valves in the mitral position at INR 2.50-3.50.

Groups

Those with mechanical prosthetic valve in the mitral po-
situation were divided into two groups: 1) Mono: patients with mono-leaflet prosthesis (or single leaflet), and 2) Bi: patients with bi-leaflet prostheses or two leaflets (or double-leaflet).

**Complications**

**Complications type**

Complications were divided into thromboembolic complications (major and minor) and bleeding (major and minor).

Thromboembolic Complication: Any kind of complication in which the patient’s records showed evidence on the occurrence of thromboembolic episodes.

Major thromboembolic complications: severe episodes requiring hospital treatment, and may or may not have left sequelae. Event types: ischemic stroke, acute arterial occlusion in limbs, prosthetic heart valve thrombosis.

Minor thromboembolic complications: Episodes of low gravity, which allowed treatment and outpatient. Event type: transient ischemic attack.

Hemorrhagic Complication: Any kind of complication in which the patient’s records showed evidence on the occurrence of bleeding episode.

Major hemorrhagic complications: severe episodes requiring hospital treatment, and may or may not have left sequelae. Event types: severe vascular hematuria, muscle bleeding in LL (bruising), vaginal bleeding (uterine), hemoperitoneum, hemopericardium, upper gastrointestinal bleeding, hemorrhagic stroke, intestinal bleeding, retroperitoneal hematoma and severe bleeding in tongue.

Minor hemorrhagic complications: Minor episodes that usually allowed treatment and outpatient. Event types: purple spots on skin, epistaxis, hematuria, vaginal bleeding, minor bleeding in stools, mild ocular bleeding, mild hemoptysis, gingival bleeding, hematoma in post-surgical pacemaker incision, mild stomach bleeding, outpatient visits on which INR greater than or equal to 7.0 were observed without effective bleeding.

Potentially hemorrhagic complications: The outpatient visits in which INR greater than or equal to 7.0 were observed were considered potentially bleeding episode, though there was no effective bleeding.

**Complications - Calculations and Actuarial curves**

In the study on the occurrence of complications calculations and actuarial curves were also used, which show the percentage of patients free of events throughout the study. To aid in the actuarial calculations, we used the Statistical Calculations For Windows V. 1.8 software developed by Dr. Domingo Marcolino Braile and Dr. Moacir Fernandes de Godoy and implemented in Power Builder 6.5 by M. S. Djalma Domingos da Silva. For construction of actuarial curves, the Microsoft Excel program was used.

**Division of patients according to the occurrence of complications for the actuarial study**

For actuarial study, patients were divided according to the occurrence of complications as follows:

Patients free of any event: free of bleeding thromboembolic events and potentially bleeding. Patients free of thromboembolic events: free of major or minor thromboembolic complications events.

Patients free of major thromboembolic events: free of major thromboembolic complications events.

Patients free of minor thromboembolic events: free of minor thromboembolic complications events.

Patients free of bleeding or potentially bleeding events: free of major or minor bleeding complications events.

It is noteworthy that in the patients who despite not having found effective bleeding, the occurrence of episodes with INR greater than or equal to 7.0 in consultation in the Ambulatory of Anticoagulation Control was considered as a complication. In actuarial study, due to the use of “event-free” terms, we preferred herein to call these episodes as “episodes or potentially bleeding events”. Patients free of major bleeding events: free of major bleeding complications events. Patients free of minor bleeding events or potentially bleeding events: considering here the increase of PT equal to or greater than 7.0 a minor complication compared to major bleeding; then the patients free of this type of event were grouped to patients free of minor bleeding events.

Patients free of minor bleeding events: patients who effectively had no minor bleeding events.

**Actuarial calculations**

For actuarial studies, the following calculations, presented in tables, were made together with the curves: Proportion of free event (PFE%); standard error (SE%), lower limit of 95% confidence interval (LLCI95%) and upper limit of 95% confidence interval (ULCI95%).

**Complications – Linearized index of occurrence of events - calculations of the number of patient-years event**

In calculating the complications patient-year, we consider the number of events. We emphasize that the same patient may have contributed to more than one event. Each patient contributed with different time intervals in the study. The sum of years of follow-up for each patient was 505.77 years, with 129 events in total.
The Linearized rates of occurrence of events were calculated:

- Bleeding events
- Major bleeding events
- Minor events
- Bleeding or potentially bleeding events
- Major bleeding events
- Minor bleeding events or potentially bleeding events
- Potentially bleeding events

To compare mono- and bi-leaflet prostheses for number of events per 100 patients/year a linear generalized model was adjusted with Poisson distribution, considering the effects of hemorrhage thromboembolism with its subdivisions, according to Wald’s multiple comparison test.

Notes
- The definitions of the events are the same as those found in relation to curves and actuarial calculations.
- For the calculations of Events Patient/Year, we included one more subdivision of bleeding complications, “potentially bleeding events” alone, or that is, outpatient visits in which INR equal to or greater than 7.0 were observed without effective bleeding.

RESULTS

Figure 1 shows the curves and actuarial calculations to patients free of any type of event to allow comparison between patients with mono- and bi-leaflet prostheses. In Figures 2, 3 and 4 we found the curves and actuarial calculations for patients free of any thromboembolic events, minor and major thromboembolic events, respectively for patients with mono- and bi-leaflet prostheses.
The results of the actuarial study with the curves and actuarial calculations from bleeding and potentially bleeding events and their subdivisions in major, minor and potentially bleeding and minor events, for both types of prostheses studied are shown in Figures 5, 6, 7 and 8.

Table 1 shows the linearized occurrence rates of events for complications and their subdivisions in number of events per 100 patients/year for patients with mono- and bi-leaflet prostheses.

**DISCUSSION**

According to “2008 focused update incorporated into the ACC/AHA 2006 - Guidelines for the manegament of Patients with valvar heart disease” [1] in patients with mechanical prosthesis in the mitral position is recommended higher level of anticoagulation than in patients with aortic prostheses based at greater risk of thrombogenicity in this location, and in any type of mechanical prosthetic mitral valve the PT (INR) should remain between 2.5 and 3.5, and this was the behavior adopted in our clinic.

We have been studying the results of oral anticoagulation in Outpatient Oral Anticoagulation Control of the Faculty of Medicine of Botucatu - UNESP for a period of 10 years on several aspects, among which, we found that only about one third of patients remain with Time prothrombin time (PT) and International Normalized ratio (INR) within the desired range in at least half of their behaviors, and that these patients were more free of occurrence of thromboembolic and bleeding complications, with a smaller number of these events in relation to the other [12].
The occurrence of temporary fluctuations in the levels of prophylactic anticoagulation in patients with mechanical heart valve prostheses leads to increased risk of embolism, since the thrombus forms more easily. When the subtherapeutic anticoagulation levels decrease, followed by increases to the desired levels occur, the thrombus becomes less adherent to the surface of the valve, so it can embolize more readily [13].

Oral anticoagulation in patients with mechanical heart valve prostheses aiming to antithrombotic prophylaxis requires differential control of prothrombin time (PT - INR or International Normalization Ratio) according to the position of the prosthesis. In the aortic position, the flow through the valve is comparatively faster and causes more stress when compared to the mitral position, especially in cases of mitral stenosis with increase of pre-existing left atrium implant. In the case of flow with marked acceleration of the blood (aortic position), platelets are activated and that the erythrocyte membranes are damaged, affecting the release of ADP-enhanced platelet activation and aggregation, with a secondary role to involvement of coagulation factors in the thrombotic potential. In the prosthesis in the mitral position, where the flow through the valve is comparatively slow, higher stasis and prolonged contact of coagulation factors with the surface of the prosthesis occurs, and in this case with the minor contribution of platelets in relation to coagulation factors in thrombogenic potential [14].

In heart valve prostheses, thrombi, mostly are formed in the suture ring, at the site of greatest tissue growth, toward the valve opening, which can result in embolism. In prosthetic cage, the thrombus may also be formed in the apex of the cage. With repeated ball impact, pieces of the thrombus may become loose, causing embolic episodes of repetition, and in this type of prosthesis thrombosis with immobilization of the ball is less common. In single and double disc prostheses, however, the thrombus may extend to local support and joints, causing their locking and embolism is the less frequent [15-17].

In the literature, assessments of the occurrence of complications by oral anticoagulation in patients with prosthetic
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Fig. 7 - Curves and actuarial data showing the percentage of patients free of minor bleeding or potentially bleeding events mBE or PB (ordinate) with time - years (abscissa) for both types of prostheses studied.
Mo = Mono-leaflet prosthesis; Bi = Bi-leaflet prosthesis; SE = standard error range; LLCI95% = lower limit of 95% Confidence Interval and ULCI95% = Upper Limit of 95% Confidence Interval

Fig. 8 - Curves and actuarial data showing the percentage of patients free from minor bleeding events mBE (ordinate) with time - years (abscissa) for both types of prostheses studied.
Mo = Mono-leaflet prosthesis; Bi = Bi-leaflet prosthesis; SE = standard error range; LLCI95% = lower limit of 95% Confidence Interval and ULCI95% = Upper Limit of 95% Confidence Interval

Heart valves are mostly retrospective due to ethics and compliance time for the occurrence of complications. In the case of the involvement of single disc prosthesis, often collections of data from earlier periods were done well, or that is, closer to the time of implantation of the prostheses periods, as shown in the case in the study by Florez et al. [6] with Omnicarbon prostheses (mono-leaflet) in aortic, mitral and mitral-aortic positions between April 1985 and May 1995 (10 years).

Similarly, in our study we had to choose a period in which there was greater availability of patients with mono-leaflet prostheses with regular controls of anticoagulation, which allowed better comparison with bi-leaflet prostheses (from January 1, 1993 to December 31 2002), this time that also corresponds most closely to routine implants of uni-leaflet prostheses. We ponder the significance of this comparison between the two types of prostheses lies mainly in the fact that many patients with single-disc prostheses continue and will continue to attend our clinic.

In this study, when comparing the actuarial curves of mitral mechanical prostheses and mono-leaflet (Figure 1) we observed that patients with mono-leaflet prostheses (FAE Mo) were more free from any kind of event with the passage of time, than patients with bileaflet prostheses (FAE Bi).

When we assess only the total bleeding events (T) (Figure 2), the position of the curves is reversed, leaving those with bi-leaflet prostheses freer from these events. The same presentation can be found for curves that consider only the major bleeding events (MBE) (Figure 3). In the case of minor bleeding events (mBE) (Figure 4), the curves are very close and the small number of patients should be considered here, which may have affected this analysis.

When assessing these curves we found that patients with bi-leaflet prostheses were most affected by complications in total, but were more free of bleeding complications.

In Figure 5, we observe that the actuarial curve of bi-leaflet prosthesis is positioned below the curve of mono-leaflet, indicating less involvement of the latter in total bleeding complications or potentially bleeding (PB). In the most serious bleeding complications, or that is, higher bleeding, there was an alternation of positions of the two curves, both positioned next and at the upper portion of the graph showing that fewer patients has been achieved in this type of complications. The
major differences between the two groups of prostheses in relation to bleeding cases, become more restricted to the minor bleeding or potentially bleeding (mB or PB) (Figure 7) and the minor bleedings (min) alone (Figure 8), and the patients with bi-leaflet valvular prostheses were more subject to these minor bleeding complications.

The results found help us to reinforce the assertion by Vongpatanasin et al. [3] on the single-disk mechanical heart valve prostheses would present more thrombogenic potential than those of double-disc.

Misawa et al. [7] assessing the experience of 14 years of use of 57 Omnicarbon prostheses (mono-leaflet) found at the end of 10 years, 80% of patients with prosthesis in the mitral position free of bleeding events.

Butchart et al. [8] presented a report of 20 years experience with Medtronic Hall prosthetic valve (mono-leaflet) in the mitral position in 796 cases. At the end of 10 years, 77% of patients remained free of bleeding events.

At the end of 10 years, Misawa et al. [8] found 92% of patients with mitral prosthesis free of severe bleeding (major).

In the study with mono-leaflet prostheses (Medtronic Hall) Butchart et al. [9] the percentage of patients free of major bleeding events after 10 years was 87% in the mitral position.

In the study by Florez et al. [6] with Omnicarbon mono-leaflet prosthetic valves in aortic, mitral and mitral-aortic positions over a period of ten years, curiously, only bleeding complications in patients with mitro-aortic prostheses are mentioned, not occurring with prostheses in mitral and aortic position alone. 97.6% of mitral-aortic patients were free of bleeding events after 10 years, with no prosthetic thrombosis. Patients with prosthesis in the mitral position also showed no bleeding complications, and 94.2% of the aortic group and 92.3% of mitral-aortic valves were free of significant bleeding after 10 years.

Ikonomidis et al. [10] published results of implantation of St. Jude Medical cardiac valve prostheses (bi-leaflet) between January 1979 and December 2000. Actuarial calculations showed that, after 10 years, 80% of mitral were free of any bleeding event, and after 20 years of follow-up, 71%, 86% of mitral were free of bleeding episodes (not specified if totals, higher or lower) after 10 years and, after 20 years, 65%.

Then, we can compare our actuarial data with some others in the literature, but in the studies cited there is no comparison between the two types of mechanical prostheses, as it was done in this study.

In the series by Misawa et al. [7], with mono-leaflet prostheses, linearized incidence rates for events in the first 5 years for any bleeding event was 2.28 per 100 patient-years in the mitral position. In major bleeding events showed 1.02 per 100 patient-years in the mitral position.

Butchart et al. [8] in the study also with mono-leaflet prostheses showed linearized incidence rates for bleeding events in 20 years from 4.0 per 100 patient-years in the mitral position. The major bleeding events were classified as ischemic strokes (ischemic stroke), and therefore shows the incidence rates of ischemic stroke of 0.8 per 100 patient-years; minor bleeding events: 3.2 per 100 patient-years and major bleeding events were 1.4 per 100 patient-years.

Florez et al. [6] assessing mono-leaflet prostheses show linearized incidence rates for events from 0 for bleeding events in patients with prostheses in mitral and aortic positions alone and 0.4 per 100 patient-years in mitral-aortic. From bleeding, the rates were 0 for mitral, 0.6 for aortic and 0.8 per 100 patient-year for mitral-aortic. In the study of Ikonomidis et al. [10] with bi-leaflet prostheses, the linearized incidence rates for bleeding events after 20 years was 3.4 per 100 patient-year for mitral. In bleeding events (not specified whether minor or major) at the end of 10 years of 2.2 per 100 patient-years for mitral, and after 20 years: 1.8 per 100 patient-years.

Brailé et al. [9], in Brazil, studied complications in 126 mitral mono-leaflet mechanical prostheses of some types (Björk-Shiley 49, 71 Liliehei-Kaster, 6 Hall-Kaster), with all patients receiving oral anticoagulants. The incidence of thrombosis and thromboembolism was 7.7 per 100 patient-years for patients with Björk-Shiley, 5.6 and 6.7 per 100 patient-years for those with Liliehei-Kaster and Hall-Kaster prostheses, respectively.

The linearized incidence rates for events found in the literature did not compare mono- and bi-leaflet prostheses. In our assessment on the number of occurrences per 100 patients/year, according to Table 1, despite the numerical differences in the P value, no statistically significant differences between the two types of prostheses studied were observed, considering thromboembolic and bleeding effects and their subdivisions, after Poisson statistical adjustment.

We should consider some limitations in this study because it was a retrospective study, in which part of the patients carries a type of heart valve prosthesis that virtually is no longer in use, and that the most important or serious complications can take a long time to occur (sometimes years), which makes difficult a prospective study in the area.

CONCLUSION

According the actuarial study we found that patients with mono-leaflet prosthetic heart valves in the mitral position were more prone to serious thromboembolic events compared to those with bi-leaflet prostheses. Patients with bi-leaflet mechanical heart valve prostheses in the mitral position were less free from bleeding accidents than patients with single-disc prosthetic valves. These differences, however, were more significant in minor bleeding episodes, without significant clinical signs.
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