Analysis of Cost-effectiveness and Budget Impact of Anticoagulants in the Treatment of Deep Venous Thrombosis in Oncology Patients

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Análise de Custo-efetividade e Impacto Orçamentário de Anticoagulantes no Tratamento da Trombose Venosa Profunda em Pacientes Oncológicos

Análisis de Costo-efectividad e Impacto Presupuestal de Anticoagulantes en el Tratamiento de la Trombosis Venosa Profunda en Pacientes Oncológicos

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Abstract

Introduction: Deep vein thrombosis is a common complication and closely related to neoplasms. New oral anticoagulants have been launched in recent years, among them rivaroxaban. **Objective**: The study analyzed the cost-effectiveness and budget impact of rivaroxaban *versus* enoxaparin. **Method**: This is a retrospective cohort, performed with oncological population from the perspective of *Sistema Único de Saúde* (National Health System). The decision tree model compared outcomes of bleeding and rethrombosis, and costs of treatment of deep venous thrombosis with rivaroxaban or enoxaparin in a time horizon of seven months. Direct costs were extracted from the SIGTAP-SUS, and the Brazilian Spreadsheet for Budgetary Impact of Health Technologies was used to evaluate the budgetary impact based in the Brazilian population of 2017 over a five-year period. The sensitivity analysis simulated scenarios for both cost-effectiveness and budget impact assessments. **Results**: One hundred and fifty-three patients were included in the cost-effectiveness analysis with several neoplasms. Rivaroxaban demonstrated no therapeutic inferiority compared to enoxaparin. The incremental cost-effectiveness ratio was R$ 5,521.71 per benefit unit spared with the new alternative, rivaroxaban. In the sensitivity analysis, rivaroxaban remained dominant. An economy in incremental budget impact of R$ 85,950,791,129.21 was demonstrated with the use of rivaroxaban over five years in comparison to the reference scenario, and this continued as the most economic option in relation to sensitivity analyzes. **Conclusion**: In this context rivaroxaban was an important therapeutic alternative.

Key words: Economics, Pharmaceutical; Neoplasms; Venous Thrombosis; Anticoagulants; Unified Health System.

Resumo

Introdução: A trombose venosa profunda é uma complicação comum e intimamente relacionada às neoplasias. Novos anticoagulantes orais foram lançados nos últimos anos, entre eles, a rivaroxabana. **Objetivo**: O estudo analisou o custo-efetividade e o impacto orçamentário da rivaroxabana *versus* enoxaparina. **Método**: Trata-se de uma coorte retrospectiva, realizada com população oncológica sob a perspectiva do Sistema Único de Saúde. Por meio do modelo de árvore de decisão, foram comparados desfechos de sangramento e retrombose, e custos do tratamento da trombose venosa profunda com rivaroxabana ou enoxaparina, em um horizonte temporal de sete meses. Custos diretos foram extraídos do Sistema de Gerenciamento da Sistema de Gerenciamento da Tabela de Procedimentos, Medicamentos, Órteses, Próteses e Materiais e Medicamentos Especiais do SUS (SIGTAP-SUS), e empregou-se a Planilha Brasileira de Impacto Orçamentário de tecnologias da saúde para avaliação do impacto orçamentário com base na população brasileira de 2017, em cinco anos. A análise de sensibilidade simulou cenários tanto na avaliação de custo-efetividade quanto na de impacto orçamentário. **Resultados**: Cento e cinquenta e três pacientes foram incluídos na análise de custo-efetividade com diversas neoplasias. A rivaroxabana demonstrou não inferioridade terapêutica comparada à enoxaparina. A razão de custo-efetividade incremental foi de R$ 5.521,71 por unidade de benefício ganho com a nova alternativa, rivaroxabana. Na análise de sensibilidade, a rivaroxabana manteve-se dominante. Foi demonstrada uma economia no impacto orçamentário incremental de R$ 85.950.791.129,21 com a utilização de rivaroxabana ao longo de cinco anos em comparação ao cenário de referência, e esta se manteve como opção mais econômica perante as análises de sensibilidade. **Conclusão**: A rivaroxabana, nesse contexto, apresentou-se como uma importante alternativa terapêutica.

Palavras-chave: Farmacoeconomia; Neoplasias; Trombose Venosa; Anticoagulantes; Sistema Único de Saúde.

Resumen

Introducción: La trombosis venosa profunda es una complicación común e íntimamente relacionada a las neoplasias. Los nuevos anticoagulantes orales fueron lanzados en los últimos años, entre ellos la rivaroxabana. **Objetivo**: El estudio analizó el Costo-Efectividad y el Impacto Presupuestario de la rivaroxabana versus enoxaparina. **Método**: En el modelo de árbol de decisión se compararon los resultados de la hemorragia y la retrombosis, y los costos del tratamiento de la trombosis venosa profunda con rivaroxabana o enoxaparina, con una cohorte retrospectiva, realizada con población oncológica bajo la perspectiva del Sistema Único de Salud en un horizonte temporal de siete meses. Los costos directos fueron extraídos del SIGTAP-SUS, y se empleó la Planilla Brasileña de Impacto Presupuestario de Tecnologías de la Salud para evaluación del Impacto Presupuestario con base en la población brasileña de 2017 en un horizonte temporal de cinco años. El análisis de sensibilidad simuló escenarios tanto en la evaluación de Costo-Efectividad y en la de Impacto Presupuestario. **Resultados**: Ciento cincuenta y tres pacientes fueron incluidos en el análisis de Costo-Efectividad con diversas neoplasias. La rivaroxabana demostró no inferioridad terapéutica comparada a la enoxaparina. La razón de costo-efectividad incremental fue de R $ 5.521,71 por unidad de beneficio ganada con la nueva alternativa, rivaroxabana. En el análisis de sensibilidad, la rivaroxabana se mantuvo dominante. Se demostró una economía em el Impacto Presupuestario incremental de R $ 85.950.791.129,21 con la utilización de rivaroxabana a lo largo de 5 años en comparación al escenario de referencia, y ésta se mantuvo como opción más económica ante los análisis de sensibilidad. **Conclusión**: La rivaroxabana, en este contexto, se presentó como una importante alternativa terapéutica.

Palabras clave: Economía Farmacéutica; Neoplasias; Trombosis de la Vena; Anticoagulantes; Sistema Único de Salud.

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INTRODUCTION

Venous thromboembolism (VTE) is a pathology that comprehends the deep vein thrombosis (DVT) and pulmonary thromboembolism (PT). Armand Trousseau initially described the relation between cancer and the blood hypercoagulable state in 1865 and ever since it has been widely discussed. The risk of a patient with cancer to develop VTE depends of innumerous variables; among them, the type of tumor, staging, moment of clinical evolution, treatment performed and intrinsic factors related to the individual[1,2].

DVT is a common complication in cancer patients and is associated to important morbidity rates and to elevated costs of treatment. In its large majority the thromboembolic events in patients with cancer are manifestations of venous thrombosis as DVT in lower limbs and/or pulmonary embolism[3-5].

Thrombosis is the second cause of death for most part of the types of neoplasms and epidemiologic studies have demonstrated a significant correlation between the occurrence of thrombosis and a worse prognosis of the disease[6,7].

International guidelines about pharmacotherapy treatment as of the *American Society of Clinical Oncology* (Asco), *European Society for Medical Oncology* (ESMO) and o *International Society on Thrombosis and Haemostasis* (ISTH) still consider low molecular weight heparin, like enoxaparin, as first line pharmacologic options for DVT treatment in oncologic patients[8,9].

Nonetheless, considering the difficulties of the management, costs, discomfort for the patients and technologic progress, new direct inhibitors oral anticoagulants of the coagulation factors were launched in the drug market as rivaroxaban, highly selective direct inhibitor of the factor rivaroxaban Xa[10]. In this scenario, there are some clinical studies as *Einstein DVT,* which demonstrate the non-inferiority of rivaroxaban in comparison with the standard therapy with enoxaparin for the treatment of DVT and rivaroxaban and *Select-D*, where rivaroxaban presented similar or better efficacy against dalteparin in oncologic patients with thrombosis[11-14].

However, some counterindications of rivaroxaban are encountered; among them, the use in patients with *clearance* lower than 15 mL/minute, liver disease associated to coagulopathy, pregnant women and breastfeeding women.

The national guideline, the *I Diretriz Brasileira de Cardio-Oncologia da Sociedade Brasileira de Cardiologia* (I Brazilian Guideline of Cardio-oncology of the Brazilian Cardiology Society), published in 2013 does not address the use of direct action oral anticoagulants (DOACS) for the treatment of cancer-associated thrombosis. In counterpart, some international guidelines already suggest the utilization of these new drugs, among them, the recommendations presented in the ISTH of 2018, where Khorana et al.[15] recommend the use of DOACS as rivaroxaban and edoxaban for the treatment of acute DVT in oncologic patients in cases of low risk of bleeding and absence of drug interactions. This recommendation is based in the fact that these drugs are grounded in robust studies addressing DVT treatment with efficacy and safety comparable to the standard therapy with low molecular weight heparin in this population[15].

Scarce publications about the economic aspect are available with cost-effectiveness analyzes and budgetary impact that include oncologic patients using rivaroxaban in SUS (National Health System). In 2016, it was conducted a cost-effectiveness analysis for a SUS federal hospital. It were considered the outcomes of effectiveness and safety of rivaroxaban and of enoxaparin in outpatient treatment, where the clinical data were extracted from a retrospective cohort of patients with gynecologic cancer and DVT. Rivaroxaban was the dominant technology with economy of R$ 7.789,61 per patient treated[16].

Under the perspective of the Health Supplementary System, a cost-effective study budgetary impact produced by da Silva[17] compared rivaroxaban with dabigatran and enoxaparin for the prophylaxis of secondary thrombosis to arthroplasty surgery of hips and knee and observed that rivaroxaban has demonstrated to be the best option for prophylaxis due to cost reduction. Another study about budget impact[18] concluded that the use of rivaroxaban to treat DVT has economic potential when compared to therapy with enoxaparin/warfarin also under the perspective of Brazil Health Supplemental System and, in addition, concluded that the main reason for the economy was the reduction of hospitalization.

Within this context, it is seen as positive the incorporation of oral anticoagulant because it facilitates the administration of the medication, reduce the number of outpatient consultations, because lab tests for dose adjustment are unnecessary , it is a non-invasive route, despite a counter-indication to patients with *clearance* lower than 15 ml/min and in period of chemotherapy[3].

Based in the arguments, the aim of this study was to evaluate the cost-effectiveness of rivaroxaban *versus* standard-therapy, enoxaparin, in a more comprehensive oncologic population and the analysis of the budgetary impact, which compared the costs of utilization of both technologies in different scenarios, from the perspective of a health manager in order to help the standardization of anticoagulants in hospitals, bearing in mind not only the costs, but the safety, effectiveness and access to new technologies.

METHOD

The methodological structure applied in this study was divided in two steps, cost-effectiveness analysis and budget impact.

Cost-effectiveness analysis

The study comprehends an analysis of a retrospective cohort of a federal hospital specialized in oncology under the perspective of the public manager. It were included in the study oncologic patients with DVT, older than 18 years old and in anticoagulant treatment with rivaroxaban or enoxaparin for at least three consecutive months. It were excluded patients referred for treatment in another institution, patients with prophylactic doses of enoxaparin, anticoagulated by atrial fibrillation, stroke and pulmonary embolism and those who failed to meet the aforementioned inclusion criteria. From January through July 2017, the charts were reviewed to obtain clinical data as age, type of tumor, staging, type of treatment received (surgery, radiotherapy and chemotherapy), date of the diagnosis of thrombosis, duration of the anticoagulant pharmacotherapy, date of the bleeding episodes and recurring DVT. Further, it was added to this study the primary data of the oncologic population analyzed by Leira et al.[16] with the objective of broadening the analysis and ensuring improved robustness to the data.

The standard prescription schema for rivaroxaban was 30 mg daily (15 mg, at every 12 hours) during 21 days, followed by 20 mg once a day in the subsequent days per the package insert; and for enoxaparin, 1 mg/kg at every 12 hours or 1.5 mg/kg/day[19]. It were analyzed the safety and effectiveness outcomes, respectively, relevant clinical bleeding and rethrombosis based in the pivotal study *Einstein e Select D*[12,14]. The classification of the bleeding episodes was based in ISTH[20] and the algorithm criteria of *Chest*[21] was used to classify rethrombosis.

A decision tree (Figure 1) was elaborated with the data collected, where it were applied the probabilities associated to the clinical events with respective costs. It was assumed a model of bleeding outcome followed by recurring DVT and it was not considered recurrence of events in a temporal horizon of seven months of treatment. Therefore, it was not necessary to apply the discount rate because of the short follow up period.

The direct costs were obtained from SUS reimbursement values recorded in the site SIGTAP-SUS "*Sistema de Gerenciamento da Tabela de Procedimentos, Medicamentos, Órteses, Próteses e Materiais e Medicamentos Especiais do SUS*" (SUS Management of the Table of Procedures, Drugs, Orthesis and Materials and Special Drugs) and notes of meeting of the online auctions of "Instituto Nacional de Câncer José Alencar Gomes da Silva (INCA)" from January to December 2017.

The number of patients who presented episodes of rethrombosis (P) for the calculation of effectiveness (E), therefore, E = (1-P)[14] were considered.

The mean of Doppler flowmetry and medical consultations in the period of seven months for every patient in each arm of the treatment, enoxaparin or rivaroxaban were applied. For the calculation of the treatment for each technology, it were added the values of utilization of every anticoagulant during seven months at the costs of tests and medical visits..

In order to evaluate the robustness of the model, it was conducted the sensitivity analysis, with univariate and bivariate different scenarios applied in a deterministic form[22]. Three scenarios were estimated to test variations of costs of technologies and/or aggravation of the bleeding and rethrombosis events.

In the first scenario, it was evaluated the reduction of 25% of the cost of technology of reference. The second and third scenario were based in the aggravation of the outcome of bleeding, with high degree of bleeding in the estimated second scenario and in the third scenario, a reduction of 50% of the cost of reference technology added to the utilization of the complex prothrombin. This study did not apply the tornado chart and did not perform the Monte Carlo probabilistic sensitivity analysis.

Budgetary impact

Two scenarios were based upon to evaluate the budgetary impact, one of reference and the other, for comparison. Each scenario consisted of two technologies in analysis with different proportions of use within the health system, representing different market conditions. It was estimated a 5-year timing horizon. The reference scenario considered the technologies during 2017 for the treatment of DVT and its respective proportions of consumption, according to the analysis of the institution's charts. For this scenario, enoxaparin presented *market share*, meaning the initial consumption of 40% and reducing to 10% until the fourth year and in the last, a 5% reduction, achieving 10% during the five years analyzed, while rivaroxaban had an initial consumption of 60%, and escalating to 90% along the last years.

The Brazilian Spreadsheet for Budgetary Impact of Health Technologies was utilized to calculate the budgetary impact developed for drugs and available for download at the website of "*Rede Brasileira de Tecnologias em Saúde*", and the Manual of Budgetary Impact[23,24].

The epidemiologic method was chosen to evaluate the budgetary impact because this method is able to estimate more comprehensively the individuals who

can benefit with the treatment. The inflation rate applied was 5%/year. Therefore, it was considered the Brazilian population of 2017 with 207,660,929 million inhabitants according to the "*Instituto Brasileiro de Geografia e Estatística* (IBGE)"[25]. The eligible population for the study was 71.4%, excluded those under 18 years and based in this population, 20% were equivalent to the rate of prevalence of DVT in cancer.

The sensitivity analysis was based in other three scenarios. The first, a reduction of 25% of the value of enoxaparin was suggested ; the second, it was reduced the consumption of rivaroxaban to 70% during the five years of analysis and in the third, it was estimated a reduction of 50% of the value of enoxaparin and a variation of 80% of the rate of consumption of rivaroxaban until the fifth year.

The results were analyzed with the statistic program Prisma® and the Microsoft Excel®, 2010. The Institutional Review Board of INCA approved the study, number CAAE: 54355416.1.0000.5274.

RESULTS

One hundred and fifty three patients were included in the analysis of cost-effectiveness, 95 in the arm of rivaroxaban and 58, in enoxaparin. Thirty nine in use of rivaroxaban and 26, enoxaparin were sourced from the study of Leira et al.[16], where oncologic patients with gynecologic tumors and DVT were evaluated.

The mean age of the patients was 57 (±13.2) years for the group of rivaroxaban, while for enoxaparin it was 54 (**±16**.5) years. Among the types of tumors analyzed, the most observed were gynecologic cancer, representing 41.0% (rivaroxaban), and 44.8% (enoxaparin), followed by breast cancer for rivaroxaban (23.2%) and lymphatic tissue and hematopoietic for enoxaparin (17.2%).

The majority of the patients presented more prevalence of cancer associated to rethrombosis in staging III or IV in 55.6% of the cases. The rivaroxaban group with 16.8% and 35.8% and enoxaparin, with 16.8% and 39.7% for stages III and IV, respectively; for 30.7% of the patients, the chart failed to report their staging.

In addition, it was analyzed the previous treatment to the anticoagulant therapy where it was observed that, of the patients who utilized rivaroxaban, 44.2% were submitted to surgery, 54.7% to chemotherapy and 21.1% to previous radiotherapy. While for the arm of enoxaparin, 29.3% were submitted to surgery, 70.7% to chemotherapy and 24.1% to previous radiotherapy. There were patients who went through more than one therapeutic modality. However, no patient was submitted to surgery concomitant to anticoagulants to reduce the risk of hemorrhage during surgery.

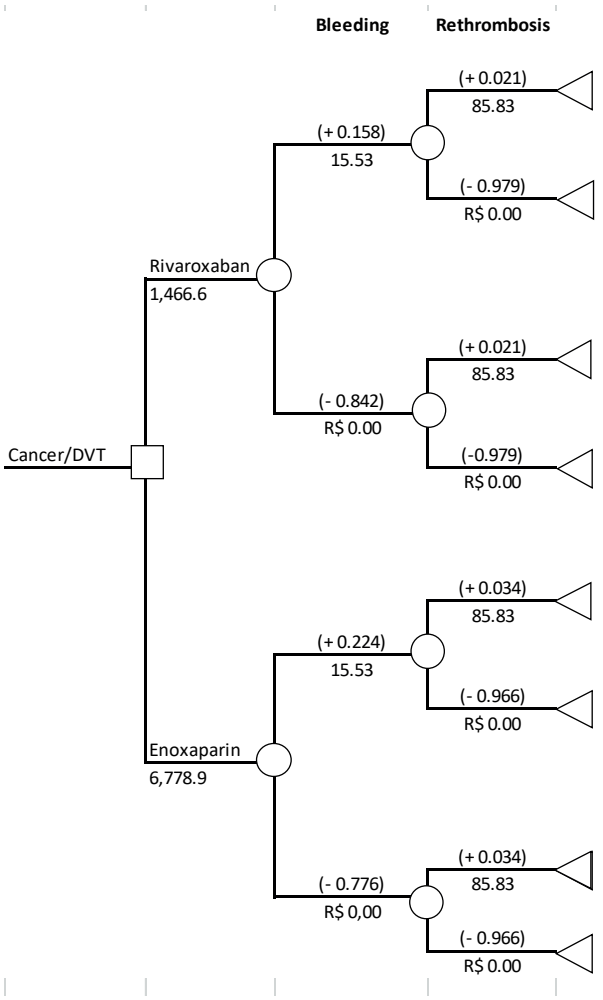

Figure 1. Schematic of the decision tree of cost-effectiveness of rivaroxaban *versus* enoxaparin, for the treatment of deep venous thrombosis in oncologic patients

Table 1 shows the direct costs with Doppler flowmetry and medical visit as well as costs with anticoagulants and treatment for bleeding and rethrombosis included in the cost-effectiveness decision tree.

It was observed that for outcomes, 15.8% of the patients had bleeding episodes with the use of rivaroxaban, while 22.4%, for enoxaparin. Nevertheless, this difference was not statistically significant. The episodes of rethrombosis represented lower frequency when compared to bleeding. It was identified rethrombosis in 2.1% of the patients who used rivaroxaban and 3.5%, enoxaparin. Both technologies presented similar therapeutic effectiveness as described in Table 1.

The cost-effectiveness analysis through the decision tree model (Figure 1) reached a cost of R$ 1,470.86 and R$ 6,785.30 per patient treated with rivaroxaban and enoxaparin, respectively during seven months. The incremental cost-effectiveness ratio observed was R$

Table 1. Parameters applied to the analysis of cost-effectiveness and budgetary impact

	Rivaroxaban n=95 (%)	Enoxaparin n=58 (%)	p-value
Bleeding	15.79	22.41	0.39
Rethrombosis	2.10	3.45	0.63
Effectiveness	(1-0.021) 0.979	(1-0.034) 0.966	-
Unitary Costs (R$)			Reference
Drugs average price	5.71/11.42*	15.80	BDOMS
Doppler flowmetry	43.50	43.50	SIGTAP
Emergency medical visit	11.00	11.00	SIGTAP
Treatment of bleeding	15.53	15.53	SIGTAP
Treatment of recurring thrombosis	85.83	85.83	SIGTAP
Number of tests	2	2	BDOMS
Number of medical visits	6	4	BDOMS
Cost of the total treatment (R$)	1,466.60	6,778.90	-

Captions: SIGTAP-SUS = Management of the Table of Procedures, Drugs, Orthesis and Materials and Special Drugs; BDOMS = Database of the Ministry of Health. **Note** *Cost considered of R$ 11.42 during the three first weeks followed by the cost of R$ 5.71/day until the end of seven months of treatment. Available from: www.comprasgovernamentais.gov.br.

5,521.71 for each patient treated with enoxaparin during seven months; this value represents an additional expense with the use of enoxaparin for the patient to benefit with the same anticoagulant effectiveness. Therefore, rivaroxaban was considered as dominant technology (Table 2).

Table 2. Incremental cost-effectiveness ratio between rivaroxaban and enoxaparin

	Rivaroxaban (R$)	Enoxaparin (R$)
Cost	1,470.86	6,785.30
Incremental Cost	-	5,314.44
Effectiveness	0.979	0.966
Incremental Effectiveness	-	-0.013
Cost effectiveness	1,502.41	7,024.12
ICER	Dominant	5,521.71

Caption: ICER = Incremental cost-effectiveness ratio.

To test the robustness of the cost-effectiveness model, sensitivity analysis (Table 3) were conducted and three scenarios proposed. In the first, it was estimated a reduction of 25% of the value of the treatment with enoxaparin. The second, it was simulated the aggravation of the bleeding outcomes, considering the value of utilization of the epsilon aminocaproic acid, hospitalization, blood count, tests, time of activated thromboplastin time (ATT) and time of prothrombin (TP). In the last scenario, reduction of 50% of the value of enoxaparin and inclusion of the use of the treatment with prothrombin complex for major bleeding. For all scenarios, rivaroxaban remained as dominant technology.

It was necessary to analyze the budgetary impact to calculate the final monthly value of each technology, which considers the value of the technology multiplied by the month units utilized for the treatment as well as its annual cost. Rivaroxaban showed final month value of R$ 285.50, annual cost of R$ 3,426.00 and additional annual of 4.4%. While enoxaparin corresponded to R$ 1,870.80 monthly, R$ 22,449.60 annual and 0.65% of annual additional. The additional value represents direct costs with approach, mild and severe adverse events, considering the annual frequency of each one and direct costs as medical consultation and tests. Rethrombosis was classified as severe adverse event and bleeding as mild adverse event. Based in the data collected from charts it was noticed, a frequency of 2% of severe adverse events with rivaroxaban and 16% of mild adverse events. For enoxaparin, a frequency of 3% of severe adverse and 22% of mild events was observed, data also obtained from the analysis of the charts. For the calculation of the costs, the same values of the cost-effectiveness analysis were adopted.

It was assumed the annual inflation rate of 4.5%[26] and temporal horizon of five years. Because of the specificity of the utilization of anticoagulants, it were not encountered market share based in scientific literature, therefore, it was assumed the share for the reference scenario based in the consumption of technologies obtained through data collected for the cost-effectiveness analysis from the charts reviewed where 60% consumed rivaroxaban and 40% consumed andenoxaparin. It was adopted an alternative scenario and for this, an estimated variation of 90% of the consumption until the fifth year of analysis.

Table 3. Analysis of deterministic univariate and bivariate sensitivity of the cost-effectiveness analysis

	Scenario 1		Scenario 2		Scenario 3	
	Rivaroxaban (R$)	Enoxaparin (R$)	Rivaroxaban (R$)	Enoxaparin (R$)	Rivaroxaban (R$)	Enoxaparin (R$)
Cost	1,470.86	5,125.59	1,614.92	6,955.23	1,624.12	3,646.71
Incremental Cost	-	3,654.73	-	5,340.31	-	2,022.60
Effectiveness	0.979	0.966	0.979	0.966	0.979	0.966
Incremental Effectiveness	-	-0.01	-	-0.01	-	-0.01
Effectiveness Cost	1,502.41	5,305.99	1,649.56	7,200.03	1,658.95	5,754.49
ICER	Dominant	-	Dominant	-	Dominant	-

Caption: ICER = Incremental cost-effectiveness ratio.
Notes: Scenario 1: Reduction of 25% of the cost of enoxaparin; Scenario 2: Escalation of the outcome bleeding; and Scenario 3: Reduction of 50% of the cost of enoxaparin plus the utilization of the complex prothrombin.

Based in the referenced budgetary analysis, it is possible to envisage a cost of R$ 552,994,083,755.33 (Table 4), from data and estimates of the current setting of utilization of two anticoagulant technologies of the hospital analyzed, while the preview with the alternative scenario suggested a cost of R$ 467,043,292,626.13 for the manager along five years. Consequently, a potential economy of the budgetary impact of R$ 85,950,791,129.21 was observed with the possible adoption of the alternative scenario, with growth from 60% to 90% of the consumption of rivaroxaban along five years.

It were adopted three scenarios for the sensitivity analysis (Table 4) of budgetary impact, based in the recommendations of the Guideline of Analysis of Budgetary Impact of the Ministry of Health[23].

For the first scenario, an estimated 25% reduction of the value of enoxaparin maintaining the increase of 5% of the consumption at every year during five years and, although the cost spared is lower than of the alternative scenario formerly determined, the alternative technology continues to indicate economy, although reduced.

The second sensitivity scenario was determined based in a lower variation of the consumption of the alternative technology. In this setting and with an estimate of 70% of consumption and even not having changes of the drugs values, rivaroxaban demonstrated an additional expense of R$ 59,710,659,587.37 during the five years of evaluation.

In the third scenario of sensitivity with the reduction of the value of enoxaparin in 50% and decrease of consumption to 80% of rivaroxaban, it was observed a potential economy of R$ 4,839,559,356.98 during the five years of analysis. In order to verify the cut of the consumption to obtain financial economy, it were tested distinguished rates of consumption of rivaroxaban in the Brazilian Chart of Budgetary Impact and it was obtained a break-even point with the consumption around 79% of the technology in study.

In order to estimate the budgetary impact of the implantation of rivaroxaban as alternative for the substitution of enoxaparin, among the measures clinically pertinent (patients with *clearance* above 15 ml/min and out of the period of chemotherapy), as choice for hospitals where standard rivaroxaban is not available, it was simulated the analysis based in the same data, but with modification of the diffusion rate of the technology in demand. The variation applied was grounded in a reference scenario where there is no standardization of rivaroxaban, where 0% of consumption of rivaroxaban and 100% of utilization of enoxaparin, and with annual gradual increase of 20% in the consumption of the technology in study with variation of 90% of its consumption. As such, it was observed the generation of economy of R$ 229,442,332,494.48 during five years in the proposed scenario.

Table 4. Sensitivity Analysis of the model of budgetary impact during five years by the epidemiologic method

Scenario 1		Scenario 2		Scenario 3	
Reference (R$)	Alternative (R$)	Reference (R$)	Alternative (R$)	Reference (R$)	Alternative (R$)
441,966,154,073.47	381,671,249,454.68	552,994,083,755.33	612,704,743,342.70	331,080,567,891.20	326,241,008,534.22

Captions: Scenario 1: Reduction in 25% of the value of enoxaparin; Scenario 2: Reduction of the consumption of the alternative technology of 70% during five years; Scenario 3: Reduction of 50% of the value of enoxaparin and variation of 80% of the consumption of the market of rivaroxaban.

DISCUSSION

In a cost-effectiveness study conducted at INCA in 2016 with patients with gynecological cancers and DVT, frequencies of outcomes of safety (bleeding) and effectiveness (rethrombosis) of rivaroxaban similar to enoxaparin's were noticed. Rivaroxaban, in the context of the study, was indicated a dominant technology for the outpatient treatment of DVT in patients with gynecological cancer[16]. These data corroborate the findings of this study even with the increase of the population and diversification of the cases of cancers analyzed.

Despite Rivaroxaban does not need routine laboratory monitoring, the mean number of tests per patients was similar and the number of consultations, higher in the group in use of rivaroxaban. This difference justifies by the yet recent implantation of the oral anticoagulant in the hospital, further to the therapy with DOACS demands extended monitoring in the initial phase of the treatment. The low mean of tests of Doppler flowmetry was because the follow up was indicated when there is some expectation of change of conduct or suspension of the anticoagulation or suspicion of new DVT[27].

In relation to the clinical outcomes, only two patients of each arm presented rethrombosis. For these cases, the medical intervention utilized were tests, consultation and pharmacological conduct. However, in literature, there is no consensus about rethrombosis management; therefore, conducts that can be adopted are dose increase, change of anticoagulant or even insertion of filter of cava vein in special situations[28].

Among the patients of the group that were anticoagulated with rivaroxaban and had bleeding episodes, 23.2% had breast cancer as base disease, but unlike expected, no patients with this type of tumor presenting episodes of rethrombosis were encountered, taking into consideration that hormone treatment for breast cancer has thrombogenic potential. Nonetheless, hormone treatment, further to increasing the risk of thrombosis, can also cause bleeding[29,30].

For patients in chemotherapy treatment, according to the standardization of the commission of anticoagulated of the hospital, it is recommended that these patients are anticoagulated with enoxaparin, having in view that new oral anticoagulant as rivaroxaban, present drug interactions with some antineoplastic at level of metabolization and can act as substrates, inducers or inhibitors of CYP3A4, influencing the pharmacotherapy treatment of the base disease[31]. In this aspect, the study indicated that 27% of the patients were anticoagulated with rivaroxaban received treatment during chemotherapy, which can represent a confounding factor, considering that it is not indicated concomitant with antineoplastic because of the pharmacokinetics interactions that can change the plasmatic concentrations of the anticoagulant, provoking possible hemorrhages or rethrombosis.

None of the patients presented major bleeding; consequently, the intervention utilized in its majority where through tests and medications without necessity of hospitalizations. During the analysis, locally base-disease associated bleeding were excluded to reduce this type of influence, adopting as outcome of bleeding all of them originated in areas other than the tumor's as recommended by Khorana et al. In addition, it is important to emphasize that, in the recommendation for patients with gastrointestinal tumor, the pharmacotherapy suggested is low molecular weight heparin because of the bleeding risk[15].

The incremental cost-effectiveness ratio encountered was R$ 5,521.71, a value that had barely suffered any influence of the outcomes evaluated, bleeding and rethrombosis that, in addition to low cost, were rarely frequent. Consequently, the therapeutic regimen and the costs of anticoagulants had a preponderant influence in the final analysis. Added to this, rivaroxaban has shown dominant in the sensitivity analysis, even with the escalation of the outcome bleeding and cost reduction of enoxaparin. These data corroborate what was encountered by Leira et al.[16] and are aligned with other Brazilian studies[17,18].

The analysis of the budgetary impact demonstrated that the rate of consumption of the new technology is the major guide of the economic setting, as bigger the consumption rate of rivaroxaban, higher is the economy generated for the public manager. The diffusion of the new technology with estimate of increase of 10% of consumption until the first four years and 5% in the last year for rivaroxaban and concomitant proportional reduction of the consumption in the more expensive treatment enoxaparin, showed strong contribution for the economic setting, producing an economy of R$ 85,950,791,129.21. This result reinforces what was published by Piedade et al.[18], whose treatment with rivaroxaban has also demonstrated a potential reduction when compared to enoxaparin/warfarin.

The sensitivity analysis of the budgetary impact has shown to be favorable for rivaroxaban. The option for reducing the value of enoxaparin in the proposed scenarios was carried out, considering a competition in the pharmaceutical market, assuming a probable reduction of the value of the comparative technology and potential repositioning in the market.

It is possible to infer, consequently, that the diffusion rates of the study technology was the biggest influencer

over the budgetary impact, since in the third scenario the value of rivaroxaban was accrued in 50% and the diffusion rate has grown until 80% and, even though, the alternative scenario was more economic.

From the perspective of an institution that does not have rivaroxaban as therapeutic option, the inclusion of a new oral anticoagulant revealed an economy of nearly 30% of the incremental budgetary impact compared to the reference scenario. Therefore, the implantation of the new technology replacing enoxaparin in situations clinically appropriate has been favorable economically, considering there was no therapeutic inferiority or safety issues with the drug. Furthermore, the pharmaceutical format of the new oral anticoagulants may positively influence the adherence of the patients to the pharmacotherapeutic treatment, having in view that the administration of enoxaparin is subcutaneous and may cause more discomfort to the patient during the process.

CONCLUSION

Rivaroxaban presented non-inferiority compared to enoxaparin, with similar frequency of bleeding and rethrombosis. The incremental cost-effectiveness ratio of R$ 5,521.71 for enoxaparin demonstrated an economy of equal value for each patient treated with rivaroxaban in seven months of treatment.

The analysis of the budgetary impact indicated a potential economy of R$ 17,190,158,225.84 per year. Based in this perspective, the substitution of enoxaparin by rivaroxaban, whenever clinically possible, is an important economic strategy and with potential benefit for the patients and hospital services.

CONTRIBUTIONS

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DECLARATION OF CONFLICT OF INTERESTS

There are no conflict of interests to declare.

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