

Health Economic Analysis of Thromboprophylaxis with Rivaroxaban and Certoparin-Sodium in Patients after Total Hip or Knee Replacement

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ABSTRACT

AIM: Postoperative deep venous thrombosis is a common complication after major orthopedic surgery. Standard prophylaxis is done by repetitive subcutaneous injections of low molecular heparin. However new oral anticoagulants became available for these indication in the last years. The aim of this prospective, comparing clinical observational study was to develop a modeling matrix considering all costs in order to allow a cost-benefit-analysis comparing anticoagulants in the post-operative administration.

MATERIALS AND METHODS: Ninety patients after total hip or knee replacement participated in this study. They were randomly divided in two groups (group - rivaroxaban, group - certoparin-sodium). Quality of life was measured by PACT-Q Score. Also compliance was analyzed by Morisky-Score. Clinical and laboratory data as well as information on occurrence and reason of readmittance to the hospital were collected.

RESULTS: The price per treatment dose of rivaroxaban is nearly two times higher compared to certoparin-sodium. In a hospital setting, a relevant part of the difference is offset by the costs for preparing the subcutaneous application of certoparin-sodium. No significant differences in clinical outcomes could be observed, but the results of the PACT-Q and the Morisky questionnaire showed clear advantages of the rivaroxaban group concerning patient treatment satisfaction and compliance.

CONCLUSION: The present study gives an idea of the consequence of the quality of life on the total costs.

INTRODUCTION

The current standard for prophylaxis of venous thromboembolism (VTE) after knee or hip replacement operation is subcutaneous injection of low molecular heparin such as certoparin-sodium. Rivaroxaban was the first drug for oral application approved for VTE prophylaxis after total hip or knee replacement. The clinical efficacy and safety of rivaroxaban was demonstrated in randomised clinical trials and is comparable with other low molecular heparin^[1]. An evaluation of the effectiveness in routine care includes associated aspects of application, as well as the subjectively perceived advantages and disadvantages for the patient.

The incidence of symptomatic deep venous thrombosis in patients after hip or knee replacement without prophylactic anticoagulation lies between 40 and 60%^[2]. There exists no clinically relevant difference between elective and fracture-conditioned interventions. In all patients after surgical interventions, injuries or acute illnesses the risk of venous thromboembolism should be considered. The indication for venous thromboembolism prophylaxis should be made risk-adapted and individually. The recommendations for the duration of prophylaxis are 28 to 35 days after a complete endoprosthesis of the hip joint and 11 to 14 days with a complete endoprosthesis of the knee joint^[3]. Currently available anticoagulants are unfractionated heparin and low molecular heparin, as well as factor-X-a-inhibitors and thrombin-inhibitors. Heparin is administered subcutaneously, while factor-X-a-inhibitors are administered subcutaneously or orally. An apparent advantage of the oral medication seems to be the avoidance of the inconvenience of a subcutaneous injection. The

administration by syringe means a higher amount of time involved for the nursing staff and for the patient higher risk for complications caused by the prick^[4]. A disadvantage of the oral medication is the higher price, while the frequency of the dosage for the examined pharmaceutical group is once a day.

According to the German Federal Office of Statistics in 2009, a total of about 213,000 primary hip endoprosthesis and 160,000 primary knee endoprosthesis were implanted in Germany^[5].

Health-economic evaluations support the fair allocation of increasingly scarce resources in the health sector. A main target is to analyse the benefits of diagnostic and therapeutic innovations for the patients and the cost payer. Only after an overall consideration of the assumed costs and benefits can the question of whether an innovative drug offers an advantage to the health system in spite of the same or higher costs be evaluated. This could appear as direct or indirect savings and a higher quality of life^[6].

The objective of the present study was to compare the total costs of the new and high priced medication rivaroxaban on the one hand with the standard certoparin-sodium on the other as thrombosis prophylaxis after knee or hip replacement. This should include associated measures and procedures and possibly arising complications, as well as the subjectively perceived advantages and disadvantages for the patient. In clinical tests, both medications proved to be adequate with regard to efficacy and safety in the medication of VTE prophylaxis. Another aim was an analysis of compliance.

MATERIALS AND METHODS

Study design

This study was prospective, comparing clinical observational study from patients' perspective. The study was in accordance to the ethical principles for medical research involving human subjects, declaration of Helsinki and acknowledged by the ethics review board of the University of Rostock (registration number A201038). All participants gave their fully informed written consent to take part in the study. Ninety patients aged from 50 to 80 years undergoing an elective knee or hip replacement were randomly assigned to a rivaroxaban (*n*=45) or a certoparin-sodium group (*n*=45). The study was conducted in an Orthopaedics Department between June 2010 and September 2011.

Cost-benefit analysis

Health economic and outcomes analysis was based on a prospective randomised clinical trial representing patients' perspective from a hospital perspective.

A process-cost analysis of VTE prophylaxis was conducted. For the estimation, 151 single subcutaneously applications were observed, including the following steps: preparation of syringe, walking to patient, brief explanation to patient and application. Time was calculated in staff costs based on local pay scale (0.21 € per minute). Prices for the pharmaceuticals and the medical devices (syringe, adaptor, hollow needle) have been taken from the german "LAUER-Taxe" (LAUER-TAXE® LAUER-FISCHER GmbH, Fürth, Germany). To measure quality of life in two patient-interviews and one interview with volunteers the Perception Anticoagulant Treatment Questionnaire (PACT-Q®)^[7] was used. It has been developed and validated as a treatment-specific instrument for the use in patients with anticoagulation therapy, and contains 27 items aggregated to four domains "expectance", "handling", "burden of disease" and "satisfaction" with anticoagulation.

To evaluate the patients' compliance, the Morisky Score^[8] was used. An online survey was conducted to get an overview of how long patients remained in hospital after hip- or knee replacement; this was addressed to 103 Orthopaedic Departments in Germany.

Statistics

All data were saved and analysed with the statistical software program SPSS 20.0 (IBM Corporation, New York, United States). The analysis of the PACT-Q® scores of patients and healthy test persons was performed in the same way. Normal distribution of characteristics in the PACT-Q® and the Morisky questionnaire was proved by Kolmogorov-Smirnov-test^[9]. If the results showed normal distribution, the *t*-test was used for dependent and non-dependent samples. In cases where the results showed non-normal distribution, the U-test (Mann Whitney) was used for non-dependent samples and the Wilcoxon-Test for dependent samples. All *p*-values are the result of two-sided statistical tests and *p* < 0.05 was considered statistically significant.

RESULTS AND DISCUSSION

Both patient groups showed no significant differences with regards to age, gender and the type of operation (Table 1). Also, no significant differences in frequency of post-operational outcome measures were observed. No bleeding complications were seen.

For the estimation of the process-costs, the application of a syringe took on average 140 seconds. For Rivaroxaban tablets, no additional time loss was incurred. In total, the cost for a single application per patient was € 5.15 for certoparin-sodium and € 5.56 for rivaroxaban, resulting in incremental costs per application of € 0.50 (Figure 1).

Significant differences were found in the PACT-Q® in favour of rivaroxaban. In three of the four domains of the PACT-Q®, significant

Table 1 Patients' characteristics.

Number of patients <i>n</i> =90	Patients		<i>p</i> -value
	certoparin-Na <i>n</i> =45	rivaroxaban <i>n</i> =45	
Age	67.3 ± 7.8	67.2 ± 7.7	0.914
Male	17	16	0.828
Female	28	29	0.828
Number hip implantation	32	20	0.199
Number knee implantation	13	25	0.199
Number duplex sonograph	2	0	0.155
Number readmittances	2	4	0.108
Number drop outs	2	2	1

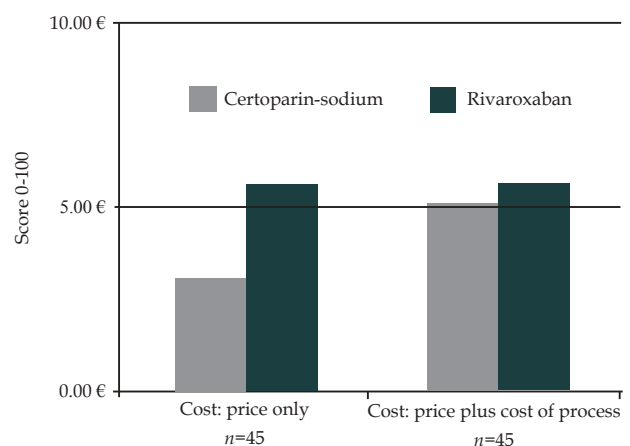


Figure 1 Price and Costs of Process at the Time of the Study: Application of Syringe/Tablet.

differences could be seen in the domains: expectance ($p < 0.05$), handling ($p = 0.049$) and treatment satisfaction with anticoagulants ($p < 0.05$). No significant difference was observed in the domain burden of disease ($p > 0.05$). In addition, a group of 90 healthy volunteers was questioned just as the patients of the study in order to add a societal perspective (Table 2).

The Morisky questionnaire showed a comparable baseline level of compliance in both groups and an improvement of compliance in the Rivaroxaban group in contrast to a decrease in the control group. However, the differences were not statistically significant (Figure 2).

It is assumed that an oral form of medication is generally better accepted than an injection and therefore the oral formulation results in increased patient satisfaction. The marketing often uses this argument to justify higher prices. However, it is important to perform adequate clinical studies to justify such an argument.

After hip or knee replacement, a difference in life satisfaction and compliance could be seen with 90 patients, which was related to two pharmaceutical application forms with substances out of the same indication group. The patients who received the rivaroxaban oral drug ($n = 45$) were significantly more content than patients with the subcutaneously administered drug during the treatment period. Patients who received the oral form of the medication noted an advantage in the handling and had higher expectations of the anticoagulants. Healthy volunteers ($n = 90$) looked at the quality of life at the examined illness and treatment and were affected slightly differently; however, in principle, the results were not contrasting. The healthy volunteers estimated clear advantages in an oral medication. In this case, the patient perspective reflected the society. The result could therefore serve as a base for decisions in the healthcare system. In the literature, Stewart *et al.*^[10] noticed that decisions should be taken after both perspectives, patients and healthy

people', had been interviewed. The combination of both perspectives would result in an appropriate view regarding the quality of life (Figure 3).

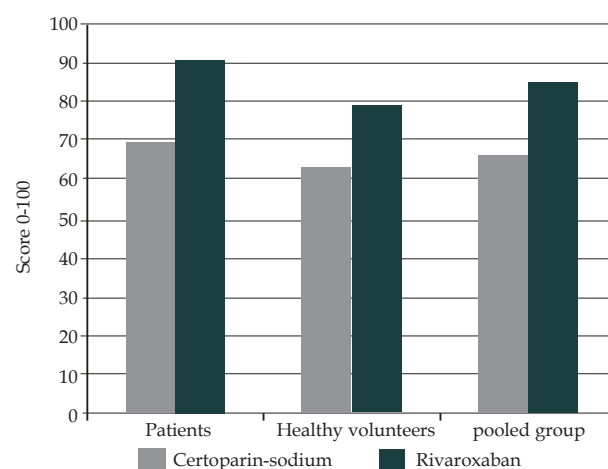


Figure 3 Evaluation of the Domains: "Expectance of Handling" of the PACT-Q® Score (Patient, Comparative group, Pool).

Wilke *et al.*^[11] analysed similar points comparable to this study: cost of process and preference. It has not yet been proven if the patients' preference is relevant from a pharmaco-economic point of view and whether it is accompanied by costs or cost savings. The question of the preference and its consequence for compliance would only become relevant if the patient is not cared for by nursing staff. An online survey, made in the context with this study, addressed 103 Orthopaedic Departments, and showed that 75% of the patients had at least 1 workday without medical attendance. Given the generally low compliance of patients of approx. 50%^[12] and the high rate of postoperative thrombosis of 40-60%, if no proper thrombosis prophylaxis is performed^[13], the consequence of the gap is clear. It has been proven in the literature by Volmer *et al.*^[14] that non-compliance can cause enormous costs. This author estimates the costs of destroyed drugs at an amount between € 8.1 and € 10.7 billion per annum.

Table 2 Pooled results of PACT-Q® questionnaire [$n = 180$, patients ($n = 90$) and healthy volunteers ($n = 90$)].

Headlines/ $n = 180$ (patients and healthy volunteers)	Satisfaction score: 1 - 100	
	Certoparin-sodium	Rivaroxaban
A ¹ : Expectance	65.6	72.8
A: Expectance of handling	69.6	90.7
B ¹ : Handling	91.3	96.3
C ¹ : Burden of disease	78.6	78.6
D ¹ : Treatment satisfaction	63.7	69.6
Average of score value	72.9	80.7

¹ A-D stand for the domain classification according to PACT-Q® questionnaire.

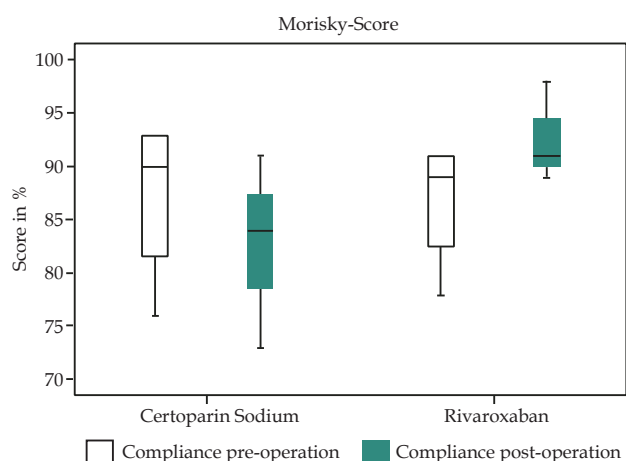


Figure 2 Patients compliance (Morisky questionnaire).

CONCLUSION

The present study gives an idea of the consequence of the quality of life on the total costs. The price per treatment dose of rivaroxaban is nearly two times higher compared to certoparin-sodium. In a hospital setting, a relevant part of the difference is offset by the costs for preparing the subcutaneous application of certoparin-sodium. In the relatively small sample of this study, no significant differences in clinical outcomes could be observed, but the results of the PACT-Q® and the Morisky questionnaire showed clear advantages of the rivaroxaban group concerning patient treatment satisfaction and compliance. Overall, VTE prophylaxis in patients after hip or knee replacement operation with rivaroxaban in inpatient treatment can be seen as cost-effective.

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CONFLICT OF INTERESTS

There are no conflicts of interest with regard to the present study.

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