

Cost-Effectiveness Analysis of Treatment Acute Deep Vein Thrombosis in Clinic of Vascular Surgery Sarajevo

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Abstract

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AIM: To compare hospital costs of acute deep vein thrombosis (ADVT) treatment in two periods of time. Evidence of repercussions on reducing costs during successful treatment. Attention was given to the necessity, costs and effectiveness of diagnostic procedures, treatment and complications.

METHODS: A retrospective analysis of data obtained from patients medical history in a period from 2000 to 2016. Model management and safe practice of ADVT care consisted of clinical examination, laboratory, colour Doppler and invasive diagnostics. In a treatment was used continuous infusion un-fractionated heparin for 40 patients from 2000th till 2006th and low molecular weight heparin for 40 patients from 2006th till 2016th. All patients were converted to oral anticoagulants.

RESULTS: When we look at the overall picture of improving the management model, safe practices and economic rationalization, we conclude that we offer better health service for the patients with ADVT at the moment, which relies on proven medical treatment trends. While we do not forget responsibility towards a society of which depends on treatment funding.

CONCLUSION: The implementation of a conceptually new model of management of ADVT did not contribute rise of the desired outcomes, but it justified the positive economic viability of introduced changes at the Clinic of Vascular surgery than the previous concept.

Introduction

Regional Committee of the World Health Organization in September 1998, which includes delegations from ministries of states members, adopted the document "Health for All in the 21st century" and 21 objective criteria's (benchmarks) to be used for measuring progress in protecting and improving health. The goal 16, Quality management of health care, focuses on outcomes as the ultimate measure of quality. By 2010, State Members shall ensure that the management of health sector from the level of health programs to the level of individual health care is oriented on individual patient's outcomes. The success of major public health strategies should be assessed regarding health

outcomes and decisions regarding alternative strategies for dealing with individual health issues, increasingly be taken by comparing health outcomes and their cost- effectiveness. All countries should have a nationwide mechanism for continuous monitoring and the development of quality care for at least ten major health conditions, including measurement of health impact, cost-effectiveness and patient satisfaction [1].

Scientific research is aimed to answer questions and establish the facts about costs using different approaches to the treatment in two periods of time in treatment model of patients with ADVT at the Clinic of Vascular Surgery Sarajevo used in the period 2006th-2016th comparing with a model of treatment of patients with ADVT in the period 2000th-2006th.

Comparison of the hospital costs and treatment models in the two periods of time. To prove which model of treatment had repercussions on the cost reduction. Researcher's attention was also given to the necessity and effectiveness of diagnostic procedures and their costs and complications and their costs.

The Council of Europe established a Commission of Experts on quality in 1995. This committee has created a large number of recommendations to the Minister of Health (adopted in 1997), which recommends that governments of member states establish systems to improve quality [2], as means that governments should develop policies and structures, where possible, which will support the development and implementation of a system for continuous assurance and improvement quality of health care at all levels. Resolution of the Council of Europe is based on the concept that the fundamental right of every individual in every community to get health care of good quality, which is defined in Article 11 of the European Social Letter on the right to health, while Article 3 of the Convention on Human Rights and Biomedicine requires that member states ensure residents' equitable access to health care of appropriate quality. Effects of any investment project can be evaluated and analysed, both regarding developing companies or institutions, as well as regarding the wider community. Institutions or companies as investors are usually interested only in direct economic effects of investments, which can be sufficiently accurately measured and expressed quantitatively, in contrast to the indirect where this is not possible. In this context, cost-effectiveness analysis is a tool for investment decisions.

Patients and Methods

The study was retrospective/prospective, descriptive and analytical, comparative, randomized and conducted in the Clinic of Vascular surgery Sarajevo Clinical Centre University of Sarajevo. The patients were divided into two groups. A group: 40 patients with acute deep venous thrombosis in the period 2006th to 2016th. B group: 40 patients with acute deep venous thrombosis in the period from 2000th to 2006th. Both groups were characterized by small variations according to age and comorbidities. Diagnostic evaluation of patients involved in- invasive and invasive procedures that each patient had been subjected. The clinical appearance of ADVT varied from absence of symptoms to massive swelling and cyanosis of the threatening venous gangrene (phlegmasia Cerulea dolens). Signs and symptoms suggestive for ADVT included pain, oedema, redness, painful sensitivity during passive dorsiflexion

(Homan's sign), fever, expressed superficial veins and peripheral cyanosis. Unfortunately, the diagnosis of ADVT based on clinical signs and symptoms is almost always wrong. More than 47 % of patients who reported to the vascular laboratory with the classical signs and symptoms were negative for ADVT after color-doppler (CD). Furthermore, more than 54% of patients with acute DVT had no specific clinical sign or symptom. The CD evaluation includes an assessment of lower limb venous compression, intra-luminal display characteristics including venous flow and luminal filling with blood.

Of these, the most widely venous non-compressibility used as an objective criterion for the diagnosis of ADVT. Non-compressibility is an excellent criterion at the proximal ADVT-e. D-dimer testing was incorporated into two general strategies. The first strategy used measure D-dimer to confirm an initial negative result of non-invasive testing and as a single procedure for reducing other diagnostics steps. Another strategy for D-dimer was in the triage of patients as an initial step for possible next diagnostic procedure. Because its limitations, D-dimer test was most valuable in combination with other diagnostic procedures, such as CD.

Therefore, patients with normal values did not require further diagnostic treatments and thus reduced consumption of vascular laboratory resources. Venography, computerized tomographic venography and pulmonary scintigraphy were used as diagnostic supplements in specific cases. In the period 2000th-2006th treatment of 40 patients usually began with continuous intravenous infusion UFH. Treatment started with intra venous (i.v.) bolus of 5.000 to 10.000 international units (IU) of UFH, followed by continuous infusion (perfusor) from 1.200 to 1.500 IU UFH per 1 hour (or fixed dose of 30.000-35.000 IU UFH in 24 hours), for 3 to 5 days. It was necessary to monitor the aPTT and INR. The aPTT had been targeted to 1.5 to 2.0 times from initial findings, and due this value doses of UFH increased or decreased. APTT was controlled every 6 hours after initiated therapy. Platelets were also counted and monitored due induced thrombocytopenia by heparin. When reduction or withdrawal of clinical signs of ADVT was noticed, we began with per oral anticoagulants, vitamin K antagonists (AVK), in a dose of 5-10 mg per 24 hours. The dose was titrated in the next 48-72 hours to target value of INR 2.0-3.0. Once these values of the INR were accomplished, heparin was continued for 24- 48 hours, and then turned off. In period of 2006th-2016th treatment began with use of LMWH enoxaparin in dose of 1 mg per kg twice in 24 hours together with AVK 10-5 mg in 24hours. INR was first monitored in patient admission and once daily till target value of INR between 2 and 4 had been accomplished.

Additional measures included treatment of any

concomitant diseases or conditions, oxygen therapy, and elevation of symptomatic extremity to reduce swelling and pain in.

Statistical analysis

All results were analysed by the statistical program SPSS version 16th 8 (SPSS Inc. Released 2007. SPSS for Windows, Version 16.0. Chicago, SPSS Inc.). The results were analysed using t-test and χ^2 test for comparison between the investigated groups. The degree of correlation is tested using the correlation coefficient Pearson or Spearman. Finally, it would apply the appropriate models of regression analysis to determine the independent association of variables. Values of $p < 0.05$ will be considered statistically significant.

Results

Patients were divided into two equal groups regarding period, group A: 40 patients from 2006th till 2016th and group B: 40 patients from 2000th till 2006th. There was the same gender ratio 18 woman and 22 men in both groups. In group A patients waited from appearance of first symptoms 55.7 hours = mean value (MV), (max = 96, min 8, Standard deviation (SD) = 33.59), in group B, MV = 87.3 hours (max = 240, min = 12, SD 60.52).

Table 1: General status and comorbidities of patients

General status and comorbidities of patients	Yes/No	A group 40 patients ADVT 2006 th -2016 th		B group 40 patients ADVT 2000 th -2006 th	
		Frequency	%	Frequency	%
Nosocomial ADVT	Y	8	20	14	35
	N	32	80	26	65
Iatrogenic ADVT	Y	3	7.5	3	7.5
	N	37	92.5	37	92.5
ADVT after trauma	Y	2	5	1	2.5
	N	28	95	39	97.5
Complication of limb fracture	Y	2	5	0	0
	N	38	95	40	100
ADVT after childbirth	Y	2	5	4	10
	N	38	95	36	90
ADVT complication after Stroke	Y	3	7.5	1	2.5
	N	37	92.5	39	97.5
Stroke as complication of ADVT	Y	1	2.5	0	0
	N	39	97.5	40	100
Plegia (hemi, para, quadro)	Y	3	7.5	1	2.5
	N	37	92.5	39	97.5
Verified oncologic disease	Y	9	22.5	2	5
	N	31	77.5	38	95
Patient on hormone replacement therapy	Y	2	5	2	5
	N	38	95	38	95
Complication of elective surgery	Y	4	10	0	0
	N	36	90	40	100
Nosocomial bleeding	Y	0	0	0	0
	N	40	100	40	100
Nosocomial Pulmonary Embolism	Y	4	10	2	5
	N	36	90	38	95
Varicose veins of lower limbs	Y	0	0	1	2.5
	N	40	100	39	97.5
Complication of surgical treatment of varicose veins of lower limbs	Y	0	0	1	2.5
	N	40	100	39	97.5
Cardiac failure	Y	3	7.5	1	2.5
	N	37	92.5	39	97.5
Death outcome	Y	1	2.5	1	2.5
	N	39	97.5	39	97.5

Hospitalization in group A lasted 13.9 days =

MV (max = 26, min = 2, SD = 5.37), in group B lasted 17.3 days =MV (max = 25, min = 17.3, SD = 3.85). All costs were in Bosnia and Herzegovina currency Convertible Mark (KM).

Table 2: The total cost of radiological diagnostics

The total cost of radiological diagnostics	Group	N	MV (KM)	SD	t	p
Color Doppler	A 2006 th -2016 th	40	62.40	10.11	16.15	0.000
	B 2000 th -2006 th	40	6.40	19.44		
Phlebography	A	40	101.07	147.52	4.33	0.000
	B	40	0.00	0.00		
Lung scintigraphy	A	40	23.00	69.87	2.08	0.041
	B	40	0.00	0.00		
Computed tomographic venography (CTV)	A	40	18.97	67.48	1.77	0.079
	B	40	0.00	0.00		
Heart ultrasound	A	40	0.00	0.00	1.00	0.320
	B	40	1.05	6.64		

Although mortality in patients with ADVT was very expected, it must be emphasized that it took place only in two deaths in the period from 2000th to 2016th in patients with diagnosed ADVT. The cause of deaths was confirmed with certainty because the autopsy procedures were carried out.

Table 3: Total costs of laboratory diagnostics

Total costs of laboratory diagnostics	Group	N	MV (KM)	SD	SG	t	p
Blood elements	A 2006 th -2016 th	40	28.70	4.42	0.70	0.82	0.413
	B 2000 th -2006 th	40	30.10	9.79	1.54		
Mineral status	A	40	36.90	5.69	0.90	0.82	0.413
	B	40	38.70	12.59	1.99		
D-Dimer	A	40	18.90	3.97	0.62	0.00	1.000
	B	40	18.90	5.69	0.90		
INR	A	40	45.30	10.06	1.59	5.92	0.00
	B	40	155.60	117.33	18.55		
APTT	A	40	73.45	16.53	2.61	5.92	0.00
	B	40	250.90	188.55	29.81		

The relationship between total costs and consumptions for analysis INR and APTT was investigated using Pearson correlation coefficient. Preliminary analyses were made to meet the assumptions of normality, linearity and homogeneity of variance. The strong positive correlation has been calculated between the consumption of the INR and the total cost ($r = 0.530, n = 80, p < 0.001$) and consumption of the APTT and the total cost ($r = 0.530, n = 80, p < 0.001$); and between the length of hospitalization and the total cost ($r = 0.932, n = 80, p < 0.001$).

Table 4: Correlation analysis of costs

Correlation analysis of costs		Hospitalization in days	INR	APTT	Total costs
Hospitalization in days	Pearson Correlation	1	0.331	0.330	0.932
	Sig. (2-tailed)		0.003	0.003	0.000
INR	Pearson Correlation	0.331	1	0.997	0.530
	Sig. (2-tailed)	0.003		0.000	0.000
APTT	Pearson Correlation	0.330	0.997	1	0.530
	Sig. (2-tailed)	0.003	0.000		0.000
Total costs	Pearson Correlation	0.932	0.530	0.530	1
	Sig. (2-tailed)	0.000	0.000	0.000	
		N	80	80	80

The Strong mutual positive correlation was found between of INR and APTT, which explains the difference and model management settings in two periods of time. We have found a strong

correlation between the medium length of hospitalization consumptions and the INR ($r = 0.331$, $n = 80$, $p = 0.003$) and between the hospitalization and consumptions for the APTT ($r = 0.330$, $n = 80$, $p = 0.003$). Significant correlation of other procedures and the total cost were not found.

Discussion

Prevention and treatment of venous thromboembolism (VTE) is a challenge we face every day by doctors and hospitalized patients. According Virchow definition from the nineteenth century, which is valid to this day, there are three factors that influence the occurrence of VTE: stasis, an abnormality in the walls of blood vessels and changes in the coagulation system. Conditions associated with high risk for ADVT are: each surgical procedure in which general anesthesia lasts 30 minutes or more particularly those that are running on legs, postpartum period, failure of the left and right chambers of the heart, fractures, injuries, chronic insufficiency of deep veins under knee, prolonged bed rest, cancer, obesity and application of estrogen. VTE has two clinical entities: deep vein thrombosis (DVT) and pulmonary embolism (PE). Accurate diagnosis of VTE is very important. If VTE is not diagnosed and treated properly, it can be fatal or cause serious complications.

The presence of VTE in the total population is 1-2%. The disease occurs depending on age, ranging from 0.03% in people younger than 50 years, to 0.4% in people over 50 years. Most studies show equal representation of disease in both sexes. Approximately 50% of patients with proximal DVT also suffer from PE, which suggests that there is a strong link between the presence of PE and DVT in the lower extremities. In the USA, every year more than 250,000 people have been diagnosed with acute DVT in at least 50,000 of them suffer a pulmonary embolism.

Standard treatment for ADVT considers anticoagulation with either LMWH or UFH as initially followed by treatment with an AVK as a long-term treatment. Cost-effectiveness of LMWH compared to UFH in the initial treatment of ADVT have been confirmed with consistent findings that therapy with LMWH has been more cost-effective compared to UFH. The major part of total costs for patients treatment were hospital days [5]. Care of patients participating in clinical trials regarding economic analyses and directly measuring the costs of interventions and outcomes may be so atypical that such results cannot be extrapolated to other settings [6]. Institutions differences, operational efficiency of health systems and participation in active clinical trials

may differ significantly from usual practice [7]. The economic evaluation of treating patients with ADVT with LMWH as compared with UFH has been published for two clinical trials [8, 9], one cost minimization study, and two cost-effectiveness analyses [10, 11]. Hull et al. showed that the LMWH strategy (tinzaparin, RR of recurrent thrombosis of 41%) dominates the UFH strategy; i.e. Recurrent thrombo-embolism with LMWH treatment strategy had 41 fewer cases of and 49 fewer deaths occur per 1,000 patients than UFH treatment strategy with savings in the health care system \$482,000 [8] (all patients were in hospital). If 37% of the patients had been treated outside the hospital's savings would increase to \$1,096,370 [9]. On the contrary to grounded opinions, the findings from Christopher J Pannucci, Lukasz Swistun, John K MacDonald, Peter K Henke, Benjamin S Brooke (Annals of Surgery 2017 January 19) question routine use of primary chemoprophylaxis in the surgical population. "These data argue strongly for a precision medicine approach to VTE chemoprophylaxis, where the intervention is guided by the risk and benefit relationship at the patient level," write Christopher J. Pannucci, MD, a plastic surgeon and an assistant professor of surgery at the University of Utah in Salt Lake City, and colleagues. The analysis of 13 studies included 14,776 surgical patients, who received "mechanical" prophylaxis (UFH, LMWH, direct factor Xa inhibitors, direct thrombin inhibitors, warfarin, dextran, and acetylsalicylic acid). Patients were stratified based on Caprini scores for VTE risk; there are 14-fold variation in risk between 0.7% - 10.7%. The incidence of VTE increased with increasing Caprini scores. "Patients with Caprini scores of ≤ 6 , which includes ~75% of surgical patients, have an unfavourable or unknown risk/benefit relationship with chemoprophylaxis." *"A 'one-size-fits-all approach' doesn't always make sense," Dr Pannucci said in a related press release. "A healthy 35-year-old is very different from someone who is 85 and has a history of clots. Our research indicates that there could be a substantial number of people who are being over-treated" [12].*

In conclusion, the implementation of a conceptually new model of management of ADVT did not contribute rise of the desired outcomes but it justified the positive economic viability of introduced changes at the Clinic of Vascular surgery Sarajevo than the previous concept. Departments of health services through fundamental changes of services should aim from the offer, health services which are determined by health service providers, to the demands, expectations and needs of patients. However, health services have not unlimited resources and should, therefore, strive for optimal balance taking into account the needs and desires of patients, expert assessments and the availability of resources. Ideal balance can be determined through the processes of communication and negotiation and

must meet the quality relationship between client/customer as patients/health professionals.

References

1. WHO Europe, Health 21 - health for all into the 21st century, European Health for All, series No. 5 Copenhagen: WHO, 1999.
2. Council of Europe, <http://www.cm.coe.int/ta/rec/1997/97r17.html>
3. O'Brien BJ, Anderson DR, Goeree R. Cost-effectiveness of enoxaparin versus warfarin prophylaxis against deep-vein thrombosis after total hip replacement. *CMAJ*. 1994;150:1083–1090. PMID:8137188 PMCID:PMC1486381
4. Menzin J, Colditz GA, Regan MM, et al. Cost-effectiveness of enoxaparin versus low-dose warfarin in the prevention of deep-vein thrombosis after total hip replacement surgery. *Arch Intern Med*. 1995;155:757–764. <https://doi.org/10.1001/archinte.1995.00430070117013> PMID:7695464
5. Gould MK, Dembitzer AD, Sanders GD, Garber AM. Low-molecular-weight heparins compared with unfractionated heparin for treatment of acute deep venous thrombosis. A cost-effectiveness analysis. *Ann Intern Med*. 1999;130(10):789-799. <https://doi.org/10.7326/0003-4819-130-10-199905180-00002> PMID:10366368
6. Drummond MF, Davies L. Economic analysis alongside clinical trials: revisiting the methodological issues. *Int J Technol Assess Health Care*. 1991;7:561–73. <https://doi.org/10.1017/S0266462300007121>
7. Ellwein LB, Drummond MF. Economic analysis alongside clinical trials: bias in the assessment of economic outcomes. *Int J Technol Assess Health Care*. 1996;12:691–7. <https://doi.org/10.1017/S0266462300010977>
8. Creekmore FM, Oderda GM, Pendleton RC, Brixner DI. Incidence and economic implications of heparin-induced thrombocytopenia in medical patients receiving prophylaxis for venous thromboembolism. *Pharmacotherapy*. 2006;26(10):1438-1445. <https://doi.org/10.1592/phco.26.10.1438> PMID:16999654
9. Schadlich PK, Kentsch M, Weber M, et al. Cost effectiveness of enoxaparin as prophylaxis against venous thromboembolic complications in acutely ill medical inpatients: modelling study from the hospital perspective in Germany. *Pharmacoeconomics*. 2006;24(6):571-591. <https://doi.org/10.2165/00019053-200624060-00005> PMID:16761905
10. Levine M, Gent M, Hirsh J, et al. A comparison of low-molecular-weight heparin administered primarily at home with unfractionated heparin administered in the hospital for proximal deep-vein thrombosis. *N Engl J Med*. 1996;334(11):677-681. <https://doi.org/10.1056/NEJM199603143341101> PMID:8594425
11. Lee AY, Levine MN, Baker RI, et al. Low-molecular-weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer. *N Engl J Med*. 2003;349(2):146-153. <https://doi.org/10.1056/NEJMoa025313> PMID:12853587
12. Pannucci CJ1, Swistun L, MacDonald JK, Henke PK, Brooke BS. Individualized Venous Thromboembolism Risk Stratification Using the 2005 Caprini Score to Identify the Benefits and Harms of Chemoprophylaxis in Surgical Patients: A Meta-analysis. *Ann Surg*. 2017.