

INPATIENT VS. OUTPATIENT: A COST COMPARISON OF THE USE OF LOW MOLECULAR WEIGHT HEPARINS DURING PREGNANCY

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Abstract

Introduction: LMWH have been shown to be effective and safe in the treatment of deep vein thrombosis. To our knowledge, this is the first analysis conducted in the Republic of Macedonia. There have been no direct comparisons of such treatment on an outpatient versus an inpatient basis.

Aim: The aim of this study is to verify the accurate cost paid by the Health Insurance Fund of Macedonia (HIFM) for the years 2014-2015 (there has been comparisons of inpatient treatment for the years 2012-2013 and outpatient treatment for the years 2014-2015) due to the fact that the HIFM changed its prescription method for these medications.

Material and Methods: For the years 2012-2013 there has been retrospective analysis, while for the years 2014-2015 a prospective cohort study has been conducted. The data was taken from the hospital's archive and it was approved by the institution's managing board.

Results: The change from inpatient to outpatient treatment for the years 2012-2013 would save 2,139,847.00 Macedonian Denars / 34,794.26 Euros to the HIFM, while for the years 2014-2015 the total saved is **2,528,820.00 Macedonian Denars / 41,119.00 Euros. (1 Euro equals 60.15 Macedonian Denars)**

Conclusion: the amendment of the medications law was financially beneficial for the HIFM.

Keywords: low molecular weight heparins, pregnancy, inpatient, outpatient, cost savings analysis

Introduction

DVT represents the development of a blood clot in a deep vein. During pregnancy, up to 80% of DVTs occur in the left leg. If left untreated, a clot can break off and travel through the circulatory system to the lungs (PE) which can be life-threatening. Fortunately, DVT and PE are treatable and even preventable among women who are most at risk. VTE which encompasses both DVT and PE, occurs in about one in every 1,000 pregnancies. While those numbers make it relatively uncommon complication, VTE actually crops up to 10 times more frequently in expecting women than in other women of the same age – and 20 times more frequently in the six weeks after birth. By eight weeks postpartum, the risk should drop back to normal [1]. The treatment and prophylaxis of VTE in pregnancy center the use of UH or LMWH because of the fetal hazards associated with warfarin, which is known to cross the placenta [2]. Neither UH or LMWH crosses the placenta, and thus there is no possibility of teratogens or

fetal hemorrhage with these drugs [3]. Although for many years UH was the standard anticoagulant used during pregnancy and into the puerperium current guidelines now recommend LMWH[4-5]. The advantages of low-molecular-weight heparin include a reduced risk of bleeding, predictable pharmacokinetics allowing weight-based dosing without the need for monitoring, and a reduced risk of heparin-induced thrombocytopenia and heparin-induced osteoporotic fractures. [6-7-8]Traditionally, patients with acute deep-vein thrombosis (DVT) have been treated in the hospital with intravenous unfractionated (UF) heparin for 5 to 7 days, followed by oral anticoagulants for 3 to 6 months [9-10-11]. Initial hospitalization was considered necessary to stabilize patients, to administer intravenous heparin, and to adjust the dose according to the results of the activated a partial thromboplastin time. The need for hospitalization of most patients with DVT has been challenged by the results of 3 recent studies that evaluated low-molecular-weight (LMW) heparins [12-13] Two factors have enabled LMW heparins to be used in the home setting to treat patients with DVT. The first relates to the effectiveness and safety of LMW heparin when administered subcutaneously once or twice daily without laboratory monitoring, and the second, to the observation that many patients with DVT do not require hospital admission [14].

Since the anticoagulant agents usually cause complications to the mother as well to the fetus, the usage of low molecular weight heparin has gradually increased. Although there are little information about their usage during pregnancy compared with the other part of the population, their usage during pregnancy is quite large during the last three decades.

The aim of the study is the pharmacy-economic analysis, more precisely the cost-profit benefit of the outpatients and the inpatients treatment. Since December, 2013 there is an amended law regarding the prescription of anticoagulant during pregnancy.

Until December, 2013 the patient, respectively the pregnant first had to visit the gynecologist who prescribed a referral for biochemical laboratory to analyze the D-dimers. After receiving the findings, the pregnant went back to the gynecologist who depending on the findings prescribed a referral to the Gynecology and Obstetrics Department. The gynecology specialist was in charge to decide about the patient's therapy. For every single patient a unique file was created. The pregnant used to take the anticoagulants at the hospital, respectively at the department. The HIFM had to pay to the hospital an amount of 380 denars (6.17 Euros) for creating of every single file for each patient, and an amount of 130 denars (2.11 Euros) for the application of every ampule. Seeing that the number of patients marking the largest increase, from December, 2013 was changed the way of prescription of the anticoagulants for pregnant women.

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The change for the prescription way of these medicines was introduced due to the large consumption of these anticoagulants. The number of ampules varies from 10 to 30 per patient, a number which is very large.

Materials and Methods

Our study represents an original research which was conducted in the Hospital of Tetova, Republic of Macedonia, respectively in the Department of Gynecology and Obstetrics

We conducted a retrospective study for the years 2012 - 2013, and a prospective cohort study during the years 2014 - 2015.

The medical charts of 941 pregnant women treated between January, 2012 and December, 2013 with the LMWH (enoxaparin, nadroparin calcium and dalteparinsodium) were reviewed.

During the period 2014-2015 the number of pregnant women receiving anticoagulant therapy was 969.

This information was recorded for each patient:

- Personal information about each patient (name and surname, birthday, living place),
- Information about the pregnancy (week and month of pregnancy, number of pregnancies),
- Time of hospitalization,
- Clinical and laboratory investigations and the diagnosis,
- Drug detail (name of the drug, dosage form, dose frequency, total cost of the drug) and

- The cost for the entire period of hospitalization.

The results were computed using Ms Excel 2007 and the SPSS (version 19.0) packages. Chi-square test was used for comparison between groups. Relationship between different parameters was measured using Pearson's correlation coefficient. P <0.05 was accepted as significant. The results were expressed as percentage/proportion either as pictorial representation.

Results

From January 1st of 2012 to December 31st of 2015, the total number of treated pregnant women with anticoagulant therapy was 1,910. Some 597 (31.3 %) of them were from urban areas, while 1,313 (68.7 %) were from rural areas. The largest number of pregnant were pregnant for the first time 1,157 (60.6 %). 1646 (86.3 %) of the pregnant women were in the third trimester of the pregnancy. The detailed information can be found at the Tables 1 and 2.

Table 1. Personal data on the total number of patients

	2012-2013 (%)	2014-2015 (%)	Total (%)	Chi square	P value
Living place					
Urban	311 (33.0)	286 (29.5)	597 (31.3)	2.77	0.10
Rural	630 (67.0)	683 (70.5)	1313 (68.7)		
Total	941 (100.0)	969 (100.0)	1910 (100.0)		
Number of pregnancies					
1	586 (62.3)	571 (58.9)	1157 (60.6)	2.2	0.33
2	184 (19.6)	206 (21.3)	390 (20.4)		
3 or more	171 (18.2)	192 (19.8)	363 (19.0)		
Total	941 (100.0)	969 (100.0)	1910 (100.0)		
Trimester					
I	25 (2.7)	27 (2.8)	52 (2.7)	4.5	0.11
II	119 (12.6)	93 (9.6)	212 (11.1)		
III	797 (84.7)	849 (87.6)	1646 (86.2)		
Total	941 (100.0)	969 (100.0)	1910 (100.0)		

The average age of the pregnant women was: 30.1±5.0.

The average of the pregnancy weeks was: 31.9±6.4

The average pregnancy months was: 8.3±1.7

Table 2. The statistical analysis about the age, the week and the month of the pregnancy

	2012-2013 Avg. ±STDV (No.=941)	2014-2015 Avg. ±STDV (No.=969)	Total Avg. ±STDV (No.=1910)	T test	P value	The dif. of the averages
Age	29.4±5.1	30.8±4.9	30.1±5.0	6.3	0.0001	-1.4
Weeks of the pregnancy	31.5±6.6	32.2±6.3	31.9±6.4	2.6	0.009	-0.8
Month of the pregnancy	8.2±1.7	8.4±1.6	8.3±1.7	2.6	0.009	-0.2

During the four years of our study, a larger number of pregnant women can be found in 2013 – 643 pregnant, while a smaller number can be found during 2012 – 298 pregnant.

In the Department of Gynecology and Obstetrics are anticoagulants which are recommended by transfusionists, and prescribed by gynecologists: Clexane (enoxaparin) 2000 IU anti-Xa in 0.2mL, Clexane (enoxaparin) 4000 IU anti-Xa in 0.4mL, Fraxiparine (nadroparin calcium) 1,900 IU anti-Xa in 0.2mL, Fraxiparine (nadroparin calcium) 2,850 IU anti-Xa in 0.3mL, Fraxiparine (nadroparin calcium) 3800 IU anti-Xa in 0.4mL [11], Fragmin (dalteparin sodium) 2500 IU anti-Xa in 0.2mL and Fragmin (dalteparin sodium) 5000 IU anti-Xa in 0.2 mL.

The prevalence of the diseases for which LMWH have been prescribed amongst pregnant inpatients.

The most common diseases which were diagnosed among pregnant women were pregnant with normal pregnancy but with high values of D-dimers, including a higher percentage of hypercoagulable pregnancy for 2012 and normal pregnancy (with high levels of D-dimers) for 2013. (Table 3.)

Table 3.The prevalence of the diseases for which LMWHs have been prescribed amongst hospitalized pregnancies.

Diagnosis	2012		2013		2012 and 2013	
	Number	Percentage	Number	Percentage	Number	Percentage
D1	119	39.93	144	22.39	263	27.95
D2	67	22.48	219	34.05	286	30.04
D3	48	16.10	181	28.14	229	24.34
D4	12	4.02	3	0.47	15	1.6
D5	4	1.34	11	1.71	15	1.6
D6	6	2.01	8	1.24	14	1.49
D7	1	0.34	13	2.02	14	1.49
D8	1	0.34	11	1.71	12	1.27
Other	40	13.44	53	8.27	93	10.22
Totali	298	100	643	100	941	100

D1 –Hyper-thrombotic pregnancy

D2 – Non-pathological pregnancy

D3 – Risky pregnancies

D4 –Hyper-thrombotic pregnancy + risky pregnancy

D5 - Pregnancy with twins + Hyper-thrombotic pregnancy

D6– Pregnancy after IVF

D7-Pregnancy after miscarriage

D8-Hyper-thrombotic pregnancy + hyper-albuminemia

In the next table are presented data about the duration of the hospitalization based on the pregnancy’s month.

Table 4. The relationship between the pregnancy month and the duration of hospitalization

Diseases	Duration of hospitalization	F test	P value
Gr. Ml. I	4.0±2.3	1.9	0.055
Gr. Ml. II	15.6±10.4		
Gr. Ml. III	19.3±11.0		
Gr. Ml. IV	18.3±11.4		
Gr. Ml. V	15.8±9.5		
Gr. Ml. VI	16.9±9.6		
Gr. Ml. VII	13.4±8.3		
Gr. Ml. VIII	14.7±9.3		
Gr. Ml. IX	14.7±8.8		
Gr. Ml. X	13.6±7.9		
Total	14.5±8.9		

The statistical analysis for the determination of the relation between the dependable variable (pregnancy month) and the independent variable (D Hospitalization days) showed that there is statistically negligible and worthless relation

at the two study years ($f = 1.9$ and $p = 0.555$). This shows that the hospitalization days have no connection with the patient's pregnancy month.

Pharmacy-economic analysis for the years 2012-2013

During the year 2012, 5,740 ampules have been completely consumed. These included 2,118 amp. of Clexane 2000, 1,021 amp. of Clexane 4000, 32 amp. of Fraxiparine 0.2, 1,402 amp. of Fraxiparine 0.3 and 1,097 amp. of Fraxiparine 0.4. For every registered patient the HIFM has paid 380 den (6.17 Euros) for file creation, 130 den (2.11 Euros) for ampule application, and the price of all ampules. The maximum number of the ampules for which HIFM paid application fee was 30. Thus, if a pregnant woman received 40 ampules only 30 were paid by the HIFM.

When from the total amount of 1,354,948.00 denars (22,031.67 Euros), are subtracted the amount of 37,263.00 denars, which was paid for the ampule application, we figure out the price which gives us details about the ampule price and the payment done by the HIFM of 380 den for every admitted patient. Since the total number of pregnant women for 2012 was 298 we calculate the amount paid by the HIFM for file creation: $298 \times 380 \text{ den} = 113,240.00$ denars. Application of each ampule: 437.263,00 denars The price for all ampules: 804.445,00 denars

During 2013 11,710 ampules had been spent in total. Of these some 2,670 amp. of Clexane 2000, 3,256 amp. of Clexane 4000, 20 amp. of Fraxiparine 0.2, 1,883 amp. of Fraxiparine 0.3, 3,560 amp. of Fraxiparine 0.4 and 321 amp. of Fraxiparine 5000. For every registered patient the HIFM had paid 380 den (6.17 Euros) for file creation, 130 den (2.11 Euros) for ampule application as well as the price of all ampules. The maximum number of the ampules for which the HIFM paid the application fee was 30, so if a pregnant woman received 40 ampules, only 30 were paid by the HIFM.

When from the total amount of 3,542,613.00 denars (57,603.46 Euros) we can subtract the amount of 1,345,024.00 denars which was paid for the ampule application. This allows us to compute the price of ampules, and the payment made by the HIFM of 380 den for every admitted patient. Since the total number of pregnant women for 2013 was 643 we calculate the amount paid by the HIFM for file creation as: $643 \times 380 \text{ den} = 244,340.00$ denars. The application of each ampule: 1,345,024.00 denars.

The outpatients' treatment with anticoagulant therapy would save the HIFM a fairly large sum of money. In that case they would not have to pay money for file creation and ampule application, but would only pay for the ampule cost:

Ampule cost: **2,757,694.00 denars / 44,840.55 Euros**

The total treatment cost: **4,897,561.00 denars / 79,635.13 Euros**

Difference: **2,139,847.00 den / 34,794.26 Euros.**

There was an amendment to the regulation on prescription of anticoagulants in December, 2013 as an emergency measure for their rational usage. With the amendment of the regulation of 2013 the HIFM only refunds 80% of the cost of the ampules with which every patient is individually supplied. The cost of 380 denars and 130 denars for application have no monetary coverage.

Table 5 .The ampule number and the cost of treatment for the years 2012-2013

2012				2013			
Therapy	Number Percentage		Total cost of the ampules	Therapy	Number Percentage		Total cost of the ampules
	No.	%			No.	%	
Clexane 2000	2,118	38.12	262,608.00	Clexane 2000	2,670	22.8	344,430.00
Clexane 4000	1,021	17.79	211,632.00	Clexane 4000	3,256	27.81	703,296.00
Fraxiparine 0.2	32	0.56	3,584.00	Fraxiparine 0.2	20	0.17	2,240.00
Fraxiparine 0.3	1,402	24.43	156,082.00	Fraxiparine 0.3	1,883	16.08	259,853.00
Fraxiparine 0.4	1,097	19.11	170,539.00	Fraxiparine 0.4	3,560	30.40	569,600.00

Fragmine 5000	0.00	0.00	0.00	Fragmine 5000	321	2.74	73,830.00
Total cost (Ampules + Application + Hospitalization) 1,354,948.00 MKD/22,031.67 Euros				Total cost (Ampules + Application + Hospitalization) 3,542,613.00 MKD/57,603.46 Euros			
Total Costs 2012 & 2013 (Ampules + Application + Hospitalization) 4,897,561.00 MKD (79,635.00 Euros)							

The prevalence of diseases for which LMWH have been ambulatory and prescribed among pregnant women

During the years of our study we have identified patients with the most diverse diagnoses. During these two years we have noticed 8 diagnoses (with the aim of comparing them with the years 2012-2013), while the rest of the diagnoses with a smaller number of patients have been collected in the section marked as "other diagnoses". The number and the percentage of the patients during the years 2014-2015 have been listed in table 6.

Table 6 The prevalence of the diseases for which LMWH have been prescribed among ambulatory treated pregnant women.

Diagnosis	2014		2015		2014 and 2015	
	Number	Percentage	Number	Percentage	Number	Percentage
D2	184	35.93	157	34.35	341	35.19
D1	124	24.22	101	22.1	225	23.22
D3	108	21.09	145	31.73	253	26.11
D4	9	1.76	2	0.44	11	1.14
D5	9	1.76	8	1.75	17	1.75
D6	7	1.37	4	0.88	11	1.14
D7	7	1.37	11	2.41	18	1.86
D8	5	0.98	7	1.53	12	1.23
Other	59	11.52	22	4.81	81	8.36
Total	512	100.00	457	100.00	969	100.00

The cost-earning analysis for inpatient and outpatient treatment for the years 2014-2015

During 2014 the number of pregnant women to whom anticoagulant therapy had been prescribed was 512. Withoutpatient treatment of pregnant women the HIFM has spent this money:

For 512 pregnant women it should have paid 380 denars for file creation: a total of **194,560.00 denars/3,136.57 Euros**.

If we calculate the amount for the application of each ampule then we have: 9,243 ampules * 130 denars for each applied ampule = **1,201,590.00denars /19,538.00 Euros**.

Therefore only for file creation the ampule payment the HIFM has spent was **1,396,150.00denars / 22,701.00 Euros**.

During 2015 the number of pregnant women to whom had been prescribed anticoagulant therapy was 457. With the outpatients' treatment of pregnant women the HIFM had spent this amount:

For 457 pregnant women should it have paid 380 denars for file creation: a total of **173,660.00 denars/2,823.73 Euros**

If we calculate the amount for the application of each ampule then we have: 7,377 ampules * 130 denars for each applied ampule = **959,010.00 denars /15,593.00 Euros**

So only from file creation and ampule payment the HIFM had spent **1,132,670.00 denars / 18,417.39 Euros**.

During these two years the total amount of savings was **2,528,820.00 denars/41,119.00 Euros**. In this case, it would be impossible to calculate the ampules cost because a large number of pregnant women, after receiving the

treatment, applied to the HIFM for refunding the ampules cost. 80% of the spent amount is refunded to them after several months. Unfortunately we don't have data about this number because this type of data was generated very late.

Discussion

Earlier conducted studies have demonstrated that LMWH has the same effect as unfractionated heparin regarding thrombosis treatment (uncomplicated thrombosis) of the deeper veins. Regarding the safety and the efficiency, we can say that LMWH offers a suitable alternative for treating the patients with venous thromboembolic. In addition, LMWH has several practical advantages, as there is no need for continuous laboratory monitoring and application by perfusion, it is enabled to treat the patient in their own homes. In this case the patient avoids the invasive methods as is the intravenous administration. Patients who suffer from deeper venous thrombosis usually should be treated as inpatients with the aim to get continuously treatment with standard heparin (un fractionated) by receiving infusions with standard ampules inside it. A study done by Levine et al., showed that Enoxaparine can be used to treat at home these patients, because it's secure and efficient. They compared two groups of patients: the first one were the patients treated with LMWH at their home and the other one were the patients treated by unfractionated heparin in hospital. The average of thromboembolism recurrence as well as the severe bleedings were very small in both groups and did not give significant differences among both groups [15-16-17]. The evidences described in various papers, talk about the cost-benefit analysis in favor of the outpatients treatment with LMWH. Until a few years ago, there were made cost-benefit analysis between the treatment with unfractionated heparin and the LMWH, while the last years there is made the analysis of cost-benefit between the inpatient and outpatients treatment, as the LMWH have proved their selves for the efficiency and safety.

A study conducted in the United States[18] concluded that outpatient treatment with heparin with LMWH is very economically. The pharmaco-economic study was made by analyzing the treatment of 102 patients. The pharmaco-economic analysis showed that the number of hospitalization days per patient dropped from 594 in 81 and from the overall cost of their treatment were saved \$72,804.00. For every single patient was saved \$2,473.00. In reviewing different literature Segal et al [19] compared the cost of the treatment with unfractionated heparin and the LMWH, and also made the comparison of inpatient against outpatient treatment for LMWH. They saw that the home treatment compared to the hospital treatment was very economically beneficial. These data also correspond well to our data. The outpatient treatment saves large amount of money for unnecessary spending like: medical file creation, ampule application (this study had calculated every single spending from laying the sheets at the medical bed to the medical gloves used by the nurse during the ampule application). According to Segal et al. outpatient treatment reduces the treatment cost up to 64%. Because in this case the ampules for every patients were provided by the hospital. The conclusion of this review is that the outpatients' treatment with LMWH is efficient, safe and cost-effective.

Conclusion

The pharmaco-economic evaluation is in favor of outpatient treatment with LMWH. The cost-earning analysis has shown that outpatient treatment costs are quite a saving compared to inpatient treatment because it avoids unnecessary costs.

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