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<sup>1</sup>Clinic for Anesthesia and Resuscitation, Clinical Center Sarajevo, Bosnia and Herzegovina

<sup>2</sup>Public Health institution, Institute for Addiction Diseases of Zenica-Doboj Canton, Zenica, Bosnia and Herzegovina

<sup>3</sup>Clinic for Nuclear Medicine and Endocrinology, Clinical Center Sarajevo, Bosnia and Herzegovina

<sup>4</sup>Acibadem Health Group, Representative Office in Sarajevo, Bosnia and Herzegovina

<sup>5</sup>Clinic for Heart and Blood vessel Diseases and Rheumatism, Clinical Center Sarajevo, Bosnia and Herzegovina

**Corresponding author:** Ismet Suljevic, Associate Professor at the Clinic for Anesthesia and Resuscitation, Clinical Center Sarajevo. Sarajevo, Bosnia and Herzegovina. Tel.: +38761184782. ORCID ID: <http://www.orcid.org/0000-0000-0002-4357-6654>.

# The Effect of Prophylactic Doses of Reviparin on the Postoperative Value of Platelets

Ismet Suljevic<sup>1</sup>, Suad Basic<sup>2</sup>, Ismana Surkovic<sup>3</sup>, Maida Turan<sup>4</sup>, Ehlimana Musija<sup>5</sup>

## ABSTRACT

**Introduction:** Low molecular weight heparin (LMWH) is used as anticoagulant in diseases characterized by possible thrombosis, as well as for thromboprophylaxis in surgery. The administration of LMWH preoperatively and postoperatively allows satisfactory thromboprophylaxis of patients undergoing surgery. Their application can reduce the number of platelets.

**Aim:** To determine what effect Reviparin has on platelet values postoperatively in patients undergoing open cholecystectomy. **Methods:** The study was conducted at the Clinic for Anesthesia and Resuscitation of the Clinical Center of the University of Sarajevo. A retrospective study was performed that included data analysis for 33 patients undergoing open cholecystectomy over a two-year period. There were 22 male and 11 female patients out of a total of 33 patients. Platelet values from laboratory findings of patient's medical history were monitored for 5 days. The values found were recorded in a table containing the patient's first and last name, gender, age and platelet value. All patients had the same endotracheal anesthesia with Propofol, Fentanyl, and Atracurium supplemented with oxygen and nitric oxide at the appropriate dose. All of the patients received same dose of 0.25ml (1432 IU) Reviparin (Clivarin) from Abbott GmbH & Co.KG, preoperatively and postoperatively. Patients undergoing laparoscopic surgery as well as patients receiving other low-molecular-weight heparin or receiving higher doses of Reviparin were excluded from the study. Statistical analysis was performed using the MedCalc v12.7 statistical package for biomedical research. **Results:** An analysis of gender representation in the total sample shows that there was 22 or 66.7% of males while there was 11 or 33.3% of female patients. Analysis of platelet values indicates that there is no statistically significant correlation with gender, but that there is a statistically significant correlation between platelet values between samples, ie. that patients who had higher preoperative values retained more platelet values even during postoperative measurements. **Conclusion:** Platelet values do not change significantly postoperatively with the use of prophylactic doses of Reviparin, after an open cholecystectomy.

**Keywords.** Reviparin, low molecular weight heparin, open cholecystectomy, platelets.

## 1. INTRODUCTION

Heparin is often used in clinical practice as prophylaxis or therapy alone or in combination with Aspirin to prevent or treat thromboembolic events. However, Heparin administration can have serious complications. Heparin induced thrombocytopenia (HIT) may be type 1 or type 2. This problem was described by Weisman and Tobin in the 1950s. Type 1 is a non-immune and type 2 is immune thrombocytopenia. HIT 1 occurs by the second postoperative day and lasts briefly in which platelet normalization occurs despite continued heparin therapy (1, 2). HIT 2 occurs from the fourth to tenth postoperative day, lasts longer and will not go away without discontinuation of heparin therapy.

It can be a serious problem in many intensive care patients with a possible lethal outcome of up to 20%. HIT should be recognized and treated urgently to prevent the development of thrombotic complications (3, 4).

## 2. AIM

To determine what effect Reviparin has on platelet values postoperatively in patients undergoing open cholecystectomy.

## 3. METHODS

The study was conducted at the Clinic for Anesthesia and Resuscitation at the Clinical Center of the University of Sarajevo. A retrospective study was performed that included data analysis for 33 patients undergoing open cholecystectomy over a two-year period. There were 22 male and

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		N	Average	Std. Deviation	Std. error	Min.	Max.
Platelets - preoperatively	Male	22	233.7273	76.58558	16.32810	118.00	374.00
	Female	11	203.6182	70.66515	21.30634	70.80	312.00
	Total	33	223.6909	74.94917	13.04698	70.80	374.00
Platelets - postoperatively 1 t=1.191; p=0.284	Male	22	204.5045	71.37280	15.21673	65.10	335.00
	Female	11	216.3364	91.22754	27.50614	72.70	393.00
	Total	33	208.4485	77.30355	13.45682	65.10	393.00
Platelets - postoperatively 2 t=0.128; p=0.722	Male	22	211.0500	78.96086	16.83451	52.10	383.00
	Female	11	222.2364	95.15826	28.69130	93.60	436.00
	Total	33	214.7788	83.36661	14.51226	52.10	436.00
Platelets - postoperatively 3 t=0.003; p=0.955	Male	22	222.5000	99.78536	21.27431	48.00	431.00
	Female	11	224.5909	97.17480	29.29930	79.50	453.00
	Total	33	223.1970	97.39754	16.95474	48.00	453.00
Platelets - postoperatively 4 t=0.079; p=0.781	Male	22	235.9500	100.58014	21.44376	48.70	462.00
	Female	11	226.2182	77.80028	23.45767	95.40	383.00
	Total	33	232.7061	92.47754	16.09827	48.70	462.00
Platelets - postoperatively 5 t=0.006; p=0.941	Male	22	234.5955	109.05282	23.25014	53.20	495.00
	Female	11	231.8182	79.33450	23.92025	123.00	371.00
	Total	33	233.6697	98.85897	17.20914	53.20	495.00
Platelets - postoperatively average t=0.006; p=0.937	Male	22	221.7200	85.82009	18.29690	53.42	395.80
	Female	11	224.2400	86.12709	25.96829	92.84	407.20
	Total	33	222.5600	84.57470	14.72257	53.42	407.20

Table 1. Shows the average values of platelets preoperatively (0), postoperatively at measurement intervals (1-5), and also the average values of all postoperative samples, according to gender.

11 female patients out of a total of 33 patients. Platelet values taken from laboratory findings from the medical histories were monitored over a 5-day period. The values found were recorded in a table containing the patient's first and last name, gender, age and platelet value. All patients underwent the same endotracheal anesthesia with Propofol, Fentanyl and Atracurium supplemented with oxygen and nitric oxide at the appropriate dose. All patients received the same dose of 0.25ml (1432 i.j.) Reviparin (Clivarina) from Abbott GmbH & Co.KG preoperatively and postoperatively.

Patients undergoing laparoscopic surgery as well as patients receiving other low-molecular-weight heparin or receiving higher doses of Reviparin were excluded from the study.

Statistical analysis was performed using the MedCalc v12.7 statistical package for biomedical research. The analyzed data were presented in table by the absolute number of cases, percentage, arithmetic mean with standard deviation and range of values. A Student's t-test was used to test for differences, along with Pearson and Spearman's correlation test in which significance level of  $p < 0.05$  was considered statistically significant.

#### 4. RESULTS

The study included 33 patients with a mean age of 59.58  $\pm$  19.4 years (Std. Error 3,383, Median 71,0 and St deviation 19,433). The youngest respondent was 22 years old and the oldest was 82 years old. An analysis of age in the total sample shows that men were more represented with 22 or 66.7% of cases than women with 11 or 33.3% of cases.

Examination of platelet values by measurements shows that platelet values during the first postoperative period

decreased, with a constant increase until the 5th postoperative period. If we compare the preoperative values with the average of 5 postoperative periods, we find that the average platelet value remained constant (Student's t-test for paired samples:  $t=0.115$ ;  $p=0.909$ ;  $r=0.756$ ;  $p=0.0001$ ). The average platelet values are shown in Table 1.

The average value of platelets in the postoperative period (average of the period 1-5) shows that it was  $222.6 \pm 84.6$  with the lowest value of 53.4 and the highest of 407, with normal distribution. Preoperative values ( $223.7 \pm 74.9$ ) did not differ significantly from the mean of postoperative values ( $222.6 \pm 84.6$ ) ( $p > 0.05$ ).

All observed variables show, according to the results of the Kolmogorov-Smirnov test, a normal distribution to test for differences between periods. Parametric statistical methods were used for gender analysis. Student's t-test with Pearson's and Spearman's correlation test.

According to the results of the Kolmogorov-Smirnov test all of the variables showed a normal distribution for testing differences between periods. Parametric statistical methods, Student's t-test with Pearson's and Spearman's correlation test, were used for gender analysis.

Analysis of platelet values by sex shows that there were no statistically significant differences in any observed period ( $p > 0.05$ ), with lower platelet values during the preoperative period, postoperatively (4<sup>th</sup> measurement) and postoperatively (5<sup>th</sup> measurement) in men, and also in other measurements in women.

Analysis of the correlation coefficients according to Spearman (by sex) and Pearson (between periods) indicates that there is no statistically significant correlation by sex, but that there is a statistically significant correlation of platelet values between periods, ie. that patients who had

more preoperative values retained more platelet values even during the postoperative periods.

## 5. DISCUSSION

Platelets are formed in the bone marrow by the division of megakaryocytes. They secrete vasoactive mediator thromboxane A<sub>2</sub>, which is essential for vasoconstriction and after injuries it forms platelet aggregation at the site of injury. Changes in platelet count and function result in coagulation disorder

Our study included 33 patients with a mean age of 59.6 ± 19.4 years. The youngest patient was 22 year old and the oldest was 82 years old. Most patients were over 50 years of age. An analysis of age in the total sample shows that men were represented in 22 or 66.7% of cases compared to women in 11 or 33.3%.

A review of the postoperative platelet values shows that the values decreased during the immediate postoperative period, with a constant increase until the 5th postoperative measurement. We can see that the average platelet value remained constant, by comparing the preoperative with the average of 5 postoperative values. Preoperative values (223.7 ± 74.9) did not differ significantly from the mean of postoperative values (222.6 ± 84.6) ( $p > 0.05$ ). Analysis of platelet values by sex shows that there are no statistically significant differences in any observed period ( $p > 0.05$ ), with lower platelet values during the preoperative period, postoperatively 4th and postoperatively 5th in men, and in other measurements in women.

Analysis of the correlation coefficients according to Spearman (by sex) and Pearson (between periods) indicates that there is no statistically significant correlation by sex, but that there is a statistically significant correlation between platelet values between periods, ie. that patients who had more preoperative values retained more platelet values even during the postoperative periods.

Platelet retention during this period was most likely caused by the short administration time of Reviparin, which did not allow the development of antibodies to the Reviparin -TF-4 complex on the platelet membrane. Initial small oscillations in the form of diminishing values postoperatively speak for HIT 1 thrombocytopenia when platelet values return near preoperative values by day 5, which is a non-immune form of HIT. Since we have limited ourselves to a five-day follow-up period for postoperative platelet counts, we are unable to speak of immune HIT 2 in our sample, which appears from day five postoperatively, when platelet values remain low over a long period of time. Similar results were reported by other studies in this field.

Thus, a study by Pallad et al included 100 patients undergoing laparoscopic cholecystectomy, which lasted 1-2 hours. The occurrence of thromboembolic complications was monitored with the prophylactic protection of low molecular weight heparin. Four cases of deep vein thrombosis (DVT) of the lower extremities have been detected in patients with otherwise increased preoperative risk (obesity, history of past thromboembolic events, and older population) (5).

The advantage of using Reviparin in the prevention of DVT with better tolerability in patients compared to Acenocoumarol was highlighted in a study by Del Bono et al. (6).

HIT 2 is the result of antibody-induced platelet activation. It is a paradoxical immune reaction that produces thrombin, leading to a hypercoagulable state and the formation of arteriovenous thrombosis.

A number of factors affect the incidence of HIT, including the type and preparation of heparin (UFH or LMWH) and the population of patients treated surgically. Although LMWH has replaced UFH, there are studies according to which the benefit of LMWH is questionable. The adverse effects of HIT can influence the decision of which of these two heparins to use. The benefit of LMWH was established in a study that tried to determine the impact of UFH and LMWH on HIT in patients treated surgically who received thromboembolic prophylaxis (7).

A study that considered the therapeutic effect of Fundaparin on HIT found that the effect is satisfactory in prophylactic doses and similar to the effect of Argatroban and Danaparoid if there were no indications of complete anticoagulation therapy (8).

The clinical course of HIT is divided into five phases: suspected HIT, acute HIT, subacute HIT A, subacute HIT B, and chronic HIT. If HIT is suspected, a 4T score is used to determine which patients are at high enough risk of HIT to discontinue heparin and initiate non-heparin parenteral anticoagulant, taking into account the patient's clinical stability, renal and hepatic function, and drug availability. In acute HIT, prophylactic platelet transfusion is avoided. Anticoagulants are recommended for up to 3 months in patients with symptomatic thromboembolism or asymptomatic DVT. Anticoagulant therapy is discontinued after platelet count recovery in patients without thrombosis. Oral anticoagulants are given after an increase in platelet count in subacute HIT A (9-12). Repeated plasmapheresis is also recommended in order to reduce immune complexes in the therapeutic treatment of HIT 2 (13).

In a study that determined the level of inhibition of factor Xa using prophylactic doses of Nadroparin and Reviparin, a statistically significant higher level of inhibition of factor Xa was found after using higher doses (0.6ml and 0.5ml) than prophylactic (0.3ml and 0.25ml), on the basis of which it is recommended to increase prophylactic doses in urologic patients with moderate risk of developing DVT and PE (14).

There is a difference in the coagulation system depending on race. Venous thromboembolism is not as common in Chinese and Caucasians. Plasma factor VII, VIII and fibrinogen concentrations are lower in Japanese than in Caucasians. The incidence of venous thromboembolism is significantly lower in Asia Pacific residents than Caucasians and African Americans (15).

In some studies investigating patients in general and orthopedic surgery, the use of Reviparin and LMWH over UFH and oral anticoagulants has been favored (16).

The multitude of different studies in the field of coagulation and thromboprophylaxis, and the complexity of this problem with the possible clinical status of patients and

the therapeutic palette, leaves a need and opportunity for further intensified targeted research in this area.

## 6. CONCLUSION

Platelet values do not change significantly after surgery with the use of prophylactic doses of Reviparin after an open cholecystectomy.

- **Patient Consent Statement:** The first author confirms that patients' consent to enroll in the study was obtained. The authors certify that they have obtained all appropriate patient consent
- **Author contribution:** First autor IS and SB have made significant contributions to the design, study design, data collection and analysis. IS, MT, EM, participated in the development of the work and the critical review of the content. Each author gave final approval of the version to be published and they are agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.
- **Conflicts of interest:** There are no conflicts of interest.
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