EVALUATION OF HEPATIC FUNCTION AMONG PATIENTS UNDERGOING TOTAL HIP ARTHROPLASTY USING ENOXAPARIN

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ABSTRACT

Objective: To evaluate hepatic changes resulting from the use of enoxaparin for prophylaxis of deep vein thrombosis among patients undergoing total hip arthroplasty. Methods: Thirty-two patients underwent elective total hip arthroplasty, using enoxaparin, and were followed up for 65 days with serial hepatic enzyme assays. Results: Changes in laboratory parameters were found in up to 75% of the patients during the study, but the parameters normalized after suspension of the treatment. No clinical evidence of hepatic lesions was found. Conclusion: The hepatic enzyme levels increase in most patients using enoxaparin, but without clinical correlation, and the levels normalize after suspension of the treatment.

Keywords – *Enoxaparin; Arthroplasty, hip; Liver failure; Venous thrombosis*

INTRODUCTION

The thromboembolic phenomena relating to the postoperative period following orthopedic surgery are well known and greatly studied. They represent high medical and hospital costs. For decades, medications with the capacity to reduce the risk of deep vein thrombosis (DVT) and its main complication, pulmonary thromboembolism (PTE), have been studied[1].

A variety of drugs are used with the aim of preventing and treating these phenomena. Among these are preparations using non-fractionated heparin and low molecular weight heparin, such as enoxaparin, cumarinic agents and new medications that are selective inhibitors of factor Xa[2].

Comparing these different drugs with each other, their efficacy for anticoagulation and safety in relation to the risk of hemorrhage has been well established in the medical literature[3-6]. However, their safety in relation to changes in liver function is not well known[7-8].

The aim of the present study was to evaluate changes in liver function among patients undergoing total hip arthroplasty with the use of enoxaparin.

METHODS

Thirty-two patients who were candidates for total hip arthroplasty were selected (18 men and 14 women). They fulfilled the following inclusion criteria: a) 18 years of age or over; b) indication for elective total hip arthroplasty; c) signing of consent statement. Their indications were for the following reasons: 22 (68.75%) due to osteoarthrosis; four (12.5%) due to avascular necrosis of the femoral head; four (12.5%) due to sequelae from a proximal femoral fracture; and two (6.25%) due to sequelae from congenital luxation of the hip. The exclusion criteria were: a) scheduling for elective bilateral hip prosthesis surgery; b) active bleeding or high risk of bleeding, thereby contraindicating treatment with low molecular weight heparin; c) contraindications regarding the drug to be used or conditions that would prevent treatment with anticoagulants; d) conditions that would contraindicate bilateral phlebography; e) pregnancy or lactation; f) among women of fertile age, nonuse of adequate contraceptive methods; g) drug or alcohol addiction; h) concomitant use of protease inhibitors for HIV treatment; i) undergoing therapy using another study product within the 30-day period preceding the start of the

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current clinical investigation; j) use of intermittent pneumatic compression during the period of active treatment; k) concomitant participation in another clinical investigation or study; l) therapy using another type of anticoagulant that could not be interrupted, or another non-permitted medication; and m) significant liver disease.

The patients' mean age was 60 years (± 14.6). The youngest patient was 20 years old and the oldest was 82 years old. None of the patients presented previous liver disease, and none of them were using medications that would alter liver function tests.

The patients followed a uniform hospital admission protocol on the day prior to surgery, with preoperative clinical and laboratory evaluations in accordance with medical indications. Samples were taken for the following liver enzyme assays: aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transpeptidase (GGT), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), total bilirubin (TB) and direct bilirubin (DB).

Use of enoxaparin was started 12 hours before the surgery, with a dose of 40 mg subcutaneously, once a day. This was maintained for 35 days. Serial assays were performed on the liver function markers: after the surgery and on the 6th, 13th, 36th and 65th days after the operation.

The following reference values were used: AST 0-41 U/l, ALT 0-45 U/l, GGT 2-65 U/l, ALP 30-125 U/l, LDH 100-220 U/l, TB 0.1-1.2 mg/dl and DB 0-0.4 mg/dl, as established by the Clinical Reference Laboratory, 8433 Quivira Road, Lenexa, Kansas, USA, where the patients' samples were analyzed.

RESULTS

In four patients (13%), one or more enzymes present elevated preoperative values (ALT and GGT). These cases were excluded from the study. During the immediate postoperative period, three patients (9%) presented elevated AST levels, two (6%) ALT, three (9%) GGT and ten (31%) LDH, i.e. a total of 13 patients (41%) with abnormalities. On the 6th day after the operation, six (19%) presented elevated AST, three (9%) ALT, 12 (38%) GGT, three (9%) ALP and five (16%) LDH, i.e. a total of 15 patients (47%) with abnormalities. On the 13th day, two (6%) presented elevated AST, four (13%) ALT, twelve (38%) GGT, five (9%) ALP and seventeen (53%) LDH, i.e. a total of 24 patients (75%) with abnormalities. On the 36th day, two (6%) presented elevated AST, one (3%) ALT, four (13%) GGT, one (3%) ALP and seven (22%) LDH, i.e. a total of 10 patients (31%) with abnormalities. On the 65th day, one patient (3%) presented elevated ALT (9%), five (16%) GGT, three (9%) ALP and none with abnormal LDH, i.e. a total of eight patients (25%) with abnormalities (Table 1).

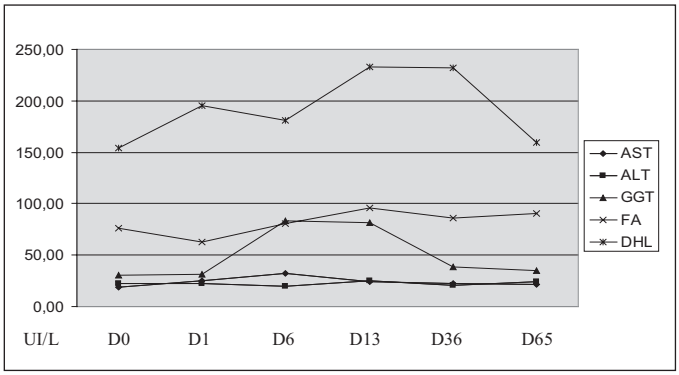
Table 1 – Elevated liver enzymes

Enzyme	Day 0	Day 1	Day 6	Day 13	Day 36	Day 65
AST	0	3 (9%)	6 (19%)	2 (6%)	2 (6%)	1 (3%)
ALT	3 (9%)	2 (6%)	3 (9%)	4 (13%)	1 (3%)	3 (9%)
GGT	3 (9%)	3 (9%)	12 (38%)	12 (38%)	4 (13%)	5 (16%)
ALP	0	0	3 (9%)	3 (9%)	1 (3%)	3 (9%)
LDH	0	10 (31%)	5 (16%)	17 (53%)	7 (22%)	0
Total	4 (13%)*	13 (41%)	15 (47%)	24 (75%)	10 (31%)	8 (25%)

AST: aspartate aminotransferase; ALT: alanine aminotransferase; GGT: gamma-glutamyl transpeptidase; ALP: alkaline phosphatase; LDH: lactate dehydrogenase

* Patients excluded from the study

The analysis on bilirubins did not demonstrate any abnormalities in any of the patients, either before the operation or during the 65 days of follow-up. None of the patients presented any signs or symptoms relating to liver function abnormalities (Figure 1).



AST: aspartate aminotransferase; ALT: alanine aminotransferase; GGT: gamma-glutamyl transpeptidase; ALP: alkaline phosphatase; LDH: lactate dehydrogenase

Figure 1 – Mean curve for liver enzymes

DISCUSSION

It is known that non-fractionated heparin presents a relationship with asymptomatic elevation of transaminases. There is no correlation between such abnormalities and clinical evidence of hepatic lesions. In published reports in the literature, liver enzyme values have become normalized after suspension of treatment with non-fractionated heparin[7].

The recently created selective inhibitors of factor Xa, which are still at the clinical study phase, have been found to present significant dose-dependent abnormalities in transaminase values during the treatment, without evident clinical abnormalities. The values become normalized after suspension of the treatment[7-9].

In our study, we found abnormalities in the liver function tests on most of the patients treated with enoxaparin, reaching 75% of them on the 13th day after the operation. In addition to the transaminases, there were elevated values for the enzymes GGT, ALP and LDH. The behavior of these abnormalities corresponded to what can be seen in the literature[3,6-8], with elevation right at the start of the treatment, a peak occurring after around two weeks of medication use, and normalization after 60 days.

The values for total and direct bilirubin remained within the limits of normality throughout the study. We did not find any reports in the literature in relation to abnormalities of bilirubin metabolism among patients using enoxaparin.

Despite the abnormalities found in this study, none of the patients presented clinical signs or symptoms relating to the elevation of liver enzyme levels. These abnormalities showed a tendency towards normalization after suspension of the treatment, with a gradual decline in the values during the follow-up.

These data resemble what can be seen in the literature[3,6-8], and it was not possible to correlate any unfavorable outcome with the elevations in the liver function tests among these patients who underwent total hip arthroplasty using enoxaparin as prophylaxis against DVT.

CONCLUSION

Most of the patients who used enoxaparin as prophylaxis against DVT/PTE presented abnormalities in laboratory tests on liver function, without clinical repercussions. These abnormalities became normalized with suspension of the treatment.

The greatest abnormality was in relation to LDH, which presented elevated values in 53% of the cases on the 13th day of enoxaparin administration.

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