



HEPARIN REBOUND PHENOMENON IN ACUTE CORONARY SYNDROMES: ADVANTAGE OF LOW MOLECULAR WEIGHT HEPARINS

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Summary. Heparin rebound phenomenon was named to illustrate unstable angina pectoris (UAP) reactivation after stopping heparin. Reinfarction clustering, as well as sharp increase of both thrombin production and activity in the early hours after heparin abandoning have been described (after thrombolysis), which has been partially attributed to heparin rebound.

The aim of the study was to show importance of problem of heparin rebound, to suggest possible directions of its avoidance and to present our own initial results with low molecular weight heparin (LMWH) Nadroparin in this context, because data on these topics have been completely lacking in our literature. Total number of pts analyzed was 45 (27 men, 18 women), average age 59.4 ± 4.3 , all of them with gastric protection with H_2 blocker.

With close in-hospital follow-up there was no heparin rebound phenomenon had negative result found, which might be related to the solid duration of therapy. In addition to careful heart rate and blood pressure control, adequate antithrombin therapy seem to improve their prognosis. Side effects were only minor haemorrhages: 5 injection site ecchymoses and 1 gingival haemorrhage, while 39 pts experienced no manifest bleeding, including 9 pts with ulcer history. There are some practical suggestions to reduce heparin-rebound phenomenon: 1) to decrease prothrombotic tendencies in the blood, unrelated to heparin; 2) to improve therapy with standard heparin and to 3) to use newer antithrombotic drugs.

We conclude that prevalence of heparin rebound can be lowered probably with adequate duration and dose of standard and LMWH, together with other suggested actions to decrease coagulation and platelet activation. Literature and own data suggest low incidence of heparin rebound phenomenon with enough long LMWH usage. They may be given with easily, with low bleeding rates, and without a need for aPTT monitoring. Thus, LMWHs for a few weeks seems justified in pts at high rethrombosis risk.

Key words: Low molecular weight heparin, heparin, rebound, acute myocardial infarction, unstable angina

Introduction

Standard heparin binds to antithrombin III via special pentasaccharide, causing conformational change, which makes arginine available that promotes binding to thrombin (1). Thrombin is essential for thrombus genesis (2), because it converts fibrinogen to fibrin; it binds to fibrin and amplifies its own production. Thrombin is important for thrombus genesis, growth, persistence and consolidation (3). Besides, thrombin is one of the most potent platelet aggregation agonists (4,5), it activates leukocytes and platelet derived growth factor (PDGF) release (6). It has been thought that standard heparin had 3 possible effects upon thrombin:

- a) in *small* doses it diminishes thrombin production;
- b) in *usual* therapeutic doses it serves as thrombin

scavenger, and

c) in *very high* doses (about 20 times usual therapeutic doses) standard heparin may even promote lysis of thrombin, already bound to fibrin (7-9).

In cardiology, heparin has been used for therapy of: unstable angina pectoris (UAP), acute myocardial infarction (AMI) deep vein thrombosis (DVT) and pulmonary embolism, heart valve thrombosis, as well as for prevention of prosthetic valve thrombosis during pregnancy etc. If administered in AMI or massive PE *with thrombolytic drug*, standard heparin doses of 5000 i.v. bolus followed by 24h i.v. infusion with 24000 IU is recommended. If standard heparin is used *without thrombolysis*, 5000 IU bolus should be given and then continuous i.v. infusion with 32000 IU/day (10). This is similar to the rule: 18 IU per kg as i.v. bolus with 80 IU/kg in 24h infusion, with aPTT control as often as

possible (optimum: each hour until aimed aPTT is achieved and then once daily) and with the correction of standard heparin dose. Oler (11) recommends aPTT 2 times control. The benefit from standard heparin lasts just as long as it is applied (12). For example, in ISIS 3 study it was found that standard heparin decreased reinfarctions (re-AMIs) for 7 days (while given). Standard heparin seems to act by preventing early reocclusion (13).

Although useful, standard heparin has some disadvantages (14,15), first one being "unpredictable bio-availability" (16,17). Another one was described by Theroux et al. (18). It is **heparin rebound phenomenon** (19), defined as **UAP reactivation after stopping standard heparin therapy**. The same author suggested that heparin rebound was not caused by hyperactive platelets (20). This was logical working hypothesis, because standard heparin had been shown to act as agonist for platelet aggregation in response to various stimuli (including ADP) (21,22), as well as by assessing the release of platelet thromboxane (23); hypothetically, activated platelet might cause restenosis after heparin cease. Rebound effect was demonstrated for hirudin, too (24).

Heparin rebound phenomenon has been described also after AMI (21). In GUSTO I study there were more re-AMI in standard heparin treated pts (12), due mostly to heparin rebound. During first few days of AMI heparin is useful because it improves infarct related artery flow. This initial benefit may disappear after end of standard heparin therapy, with subsequent reocclusion: Re-AMI clustering in the early hours after heparin cease has been described (in thrombolized pts). Probable explanation is that rethrombosis may take place after heparin cease due to high thrombogenicity of residual thrombus and persistence of other procoagulant factors.

Furthermore, to our opinion, chances for heparin rebound to occur are probably higher in AMI. Firstly, thrombus has been more frequently found in coronary artery in AMI pts than in UAP pts, and thrombus activates coagulation strongly, predisposing for heparin rebound. Secondly, fibrinolytic therapy, given in AMI but not in UAP, is thrombophilic (25-27), *per se* (6), by: 1) plasminogen - mediated activation of F XII and platelets; 2) release of PAI; 3) causing "plasminogen steal". Besides, thrombolysis itself releases active thrombin, previously fibrin-adsorbed (27,28). Thrombolysis also activates F V, and allows platelets & F Xa to resist the action of heparin (29). Thrombosis and thrombolysis are dynamic, simultaneous and opposing processes; immediate increase in thrombin generation and activity with thrombolysis necessitates the simultaneous administration of an antithrombotic drug with the lytic drug to maximize the extent of thrombolysis (30). Interestingly, in TIMI 11A, there was no rebound phenomenon after dose reduction or discontinuation of treatment with LMWH enoxaparin (31).

Braunwald's group (32) underlines the importance of haemostatic impact: 3 markers of procoagulant activity

(fibrinopeptid A /FPA/, thrombin-antithrombin complex /TAT/, prothrombin fragment 1.2 /PF1.2/) as well as fibrinolytic activity marker (B beta 1-42) were good predictors of mortality, coronary artery flow, haemorrhage and recurrent ischaemia. The higher FPA and PF1.2, the worse was the prognosis.

Logical explanation for heparin rebound phenomenon is that standard heparin antagonizes strong procoagulant tendencies (persistence of ruptured plaque with exposure of collagen and lipid gruel, thrombogenic surface of the residual thrombus, increased shear rate and turbulent flow created by the residual (atherosclerotic) stenosis (especially if high-grade), absence of normally functioning endothelium (and thus less prostacyclin, EDRF, etc.), persistent platelet activation, high catecholamine levels, etc.) (28). After standard heparin cease, an important part of protection against thrombogenesis disappears and thrombogenic tendencies might predominate. Such a concept is supported by studies, suggesting that thrombin activity (as measured through FPA) is diminished by standard heparin, but that PF1.2 (and, thus, thrombin level and thrombophilia) persist for more than 6 months (29).

In AMI and UAP pts, standard heparin reduces FPA (thrombin activity), without any important influence on PF1.2 (thrombin generation), because tissue factor persists (29). The end of standard heparin therapy in an individual patient leads to sharp increase of both thrombin genesis and activity-upon fibrinogen. The short interval from standard heparin cease to heparin rebound represents the consequence of relatively short standard heparin half life (1 hour) in circulation.

Aim of the work

The aim of the study was threefold: 1) to point out importance of heparin rebound; 2) to suggest possible directions of its avoidance and 3) to present our own initial results with low molecular weight heparin (LMWH) Nadroparin in this context. There has been not a single report in our literature about these subjects.

Patients and Methods

There were 25 AMI and 20 UAP pts analyzed, who were treated with LMWH and followed during hospital stay in Department for Cardiovascular Disease, Clinical Center, Niš, from may 1996 on. Most of them were followed out of CCU. Braunwald's classification of UAP was used (33). Pts with important part of secondary ischaemia (i.e. pronounced anaemia) were excluded, because of less probability of coronary artery thrombosis. Pts with post-AMI UAP were not extracted from AMI group. Treatment duration was individualized (from 3 to 20 days).

Total number of pts analyzed was 45 (27 men, 18 women), average age 59.4 ± 4.3 years. Therapy applied

consisted usually of acetylsalicylic acid, standard heparin, analgesic, nitrate (i.v. at the beginning), oxygen, beta blocker, ACE inhibitor and streptokinase (for AMI patients). All AMI patients had characteristic clinical picture, enzymatic, ECG and echocardiographic findings.

The study was open and observational. Special attention was given to heparin rebound phenomenon. LMWH Nadroparin (Fraxarin by Hemofarm Vršac and Sanofi, France) was used. The doses from 1–2 syretes of 0.3 ml (3075 IU) once/twice daily were applied, according to the risk/benefit profile of each patient.

Results

Our intention was to include UAP pts with primary UAP, with both worsening angina and recent rest pain. Such pts have high likelihood of coronary artery thrombosis (Table 1).

Table 1. Classes of UAP among our patients (pts.)

Class	Severity	Clinical Circumst.	Intensity of Th
Class I, A, 1	de novo/crese.	3 pts secondary	0 pts minimal
Class II, B, 2	rest subacute	5 pts primary	20 pts standard
Class III, C, 3	rest acute	12 pts post-AMI	0 pts maximal

There was slight predominance of anterior wall AMIs (56%) vs inferior wall AMIs (44%), which was considered reasonable. Namely, higher probability of left ventricular thrombosis and/or congestive heart failure imposed a need for (extended) prevention with LMWH.

With increasing experience as well as support from trials, we started to use LMWH not only following StH (33 pts), but as initial anticoagulant therapy as well (12 pts).

Based on the individual risk/benefit ratio, various Nadroparin doses were applied (Fig. 1).

Duration of LMWH Th depended upon clinical course of CAD, number of risk factors for DVT / left atrial / left ventricle thrombosis, availability of Nadro-

parin, etc. (Fig. 2).

Close follow-up detected no heparin rebound phenomenon, which might be related to adequate duration of therapy.

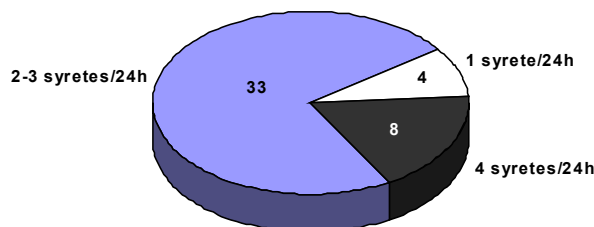


Fig. 1. LMWH doses: numbers of Fraxarin syretes (3075 UI) daily

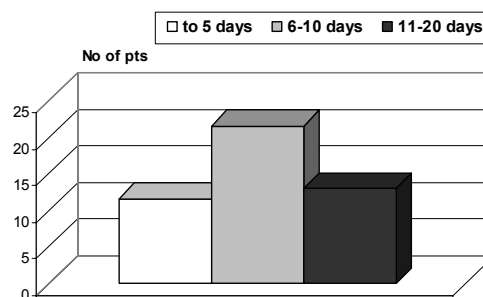


Fig. 2. Duration of LMWH (Fraxarin) therapy

Out of all 20 UAP pts studied only one had "destabilization" of CAD.

The most important and feared complication of heparin Th has been bleeding. To the best of our attention, only minor signs of haemorrhage were found: injection site ecchymoses in 5 pts and gingival haemorrhage in one patient. Majority of pts had no bleeding complications (39 pts).

Gastrointestinal bleeds have been most frequently recorded (from transfusion-requiring ones) in trials, with subsequent contraindication to aspirin for long period of time. Knowing hazards of bleeding to AMI / UAP patients, as well as risk of aspirin avoidance, we

Table 2. Practical suggestions for pharmacotherapy to reduce heparin rebound phenomenon

I) To decrease prothrombotic tendencies in the blood, unrelated to heparin

- Th against Plt aggregation (ASA and newer medicaments, i.e. GP lib/IIIa receptor inhibitors);
- Th against pain, heart Th, sedation (to decrease catecholamines levels);
- Th against spasm of coronary arteries;
- Th against increased blood viscosity (most important: elevated red blood cell count and fibrinogen);
- Th against heart failure (do decrease stasis);

II) To improve Th with StH

- start StH Th simultaneously with fibrinolytic drug;
- adjust StH dose to ensure aimed aPTT (60–70 s or twice control) within 24 hours;
- adjust StH dose once daily according to aPTT;
- count Plt to avoid heparin-induced thrombocytopenia, which paradoxically may cause thrombosis;
- adjust StH Th duration according to individual risk for rethrombosis;
- overlap StH and warfarin adequately (if warfarin is needed);
- decrease StH dose gradually (if warfarin Th is not intended).

III) Use newer antithrombotic drugs

- LMWHs for a longer period (if needed), at least alter StH;
- Hirudin / hirulog

administered routinely prophylactic H₂ blocker Ranitidine. Not a single patient reported either ulcer complaints or had haematemesis / melena, although 9 pts had positive history for peptic ulcer. We hold this for very important result in our patients prone to stress ulcer, especially in presence of congestive heart failure.

To test logical hypothesis that the longer LMWH therapy, the more bleedings would arise, analysis showed only a trend toward such expectation.

Discussion

Thrombolysis represents the crucial advance in AMI treatment. In our coronary care unit, the number of AMI pts receiving thrombolysis has been for the years around 50% of all AMI pts, including these without indication for fibrinolytics (ST depression, late arrival, etc.), as well as those with contraindication for it. The percentage of thrombolysed AMI pts was better than reported for the other institutions in our country (34). Cardiologists have been often the witnesses of UAP reactivation and re-AMI in (post)coronary unit. It has been one of the most important problems in acute coronary syndrome treatment, which has been the single most important cause of death in many countries. Among the numerous risk factors for unwanted course of the disease, heparin rebound phenomenon takes its place, which is very difficult to evaluate, having in mind complex UAP/AMI pathogenesis and individual characteristics of pts. Many factors participate in reocclusion except heparin rebound. Thus, its incidence is logical to expect to be less than reocclusion incidence, which varies.

Incidence of reocclusion was 4.8% at 5-7 days (35). From 5–15% reocclusions were reported for the first week, approximately half occurs in the first 24 hours (26). In TAMI A infarct related artery reocclusion occurred in 14–18%, associated with greater mortality rate and in GUSTO recurrent ischaemic event occurred in 19% and re-IM in 4% after 1 month. (36). After successful thrombolysis reocclusion accounts for 12–15%, but can be reduced to 5-7% with proper therapy (11). Reocclusion of the culprit coronary artery occurs in up to one third of pts during the first 3 months after AMI / unstable angina (37). Interestingly, in AMI, mortality during the first days following randomization was identical among the groups, with or without aspirin, which suggested ASA action was rather one of prevention against reocclusion than one of accelerating dissolution of the thrombus (38).

Heparin rebound may be unrecognized in many pts (21). Complete occlusion may occur clinically silent. To our opinion, heparin rebound can be detected at bedside either if it is very pronounced by itself, or if it is relatively weak, but enough to augment already strong pro-coagulant tendencies. Of course, having rebound in mind, we ought to apply heparin properly long and to decrease its dose gradually, which is currently not in our

routine.

To our opinion, there has not been a single adequate study of heparin rebound so far. Namely, such one should have complete pro- and anticoagulant monitoring (FPA, PF1.2, TAT, D-dimer, FDP, fibrinogen, CRP, etc.), as well as heparin activity measurements (including anti IIa and anti Xa), together with ECG monitoring and 2–3 coronary angiography in first month following AMI /UAP in patients randomized to longer and shorter period of heparinization, as well to standard and LMW heparin (2 × 2 design, double-blinded).

Therapy for heparin rebound in AMI pts, usually consists of heparin reinfusion, without the need for additional fibrinolytic (21). If it fails, one usually has to proceed to fibrinolysis. Of course, prevention is preferred approach (39) and one of possibilities has been to apply LMWH instead of standard heparin. LMWHs were reported to have less rebound phenomenon (31). It sounds reasonable, because LMWHs can be easily administered for *long period* of time (case reports up to 6 years), allowing time for thrombophilia to diminish. Longer treatment with LMWH was used, for example, in TIMI 11A trial: self administration at home was well tolerated, and no rebound was noted (31). Even in such delicate situation, as in 50 pregnant women with recurrent fetal loss, longer LMWH (self - administered at home) therapy was safe (and effective), in combination with aspirin (40).

LMWHs have been known for about 20 years, with Nadroparin (Fraxarin) as the first one (17). LMWHs have molecular weight from 4000–6000 daltons, which is about 3 times less than that of standard heparin, from which they are produced, by means of various methods of purification. LMWHs act more on activated coagulation FXa than on FIIa. Thus, the bleeding tendency is less for LMWH than for standard heparin, which acts equally upon FXa and FIIa.

LMWHs have better absorption as well as longer effect in comparison to standard heparin (41,42). It allows them to be applied s.c., which in turn, permits early rehabilitation to acute coronary syndrome patients. Also, LMWHs have been more comfortable to pts (43,44), because with standard heparin i.v. infusions have been preferred (in cardiology). In addition, LMWHs become not bound to plasma proteins and endothelium as much as standard heparin does (25). Thus, the bioavailability of LMWHs is higher (around 90%) and the antithrombotic effect much more predictable (25). As a result, LMWHs do not require aPTT controls and dose adjustments even in prolonged treatment. This decreases efforts of medical staff while working with LMWHs. Reports suggest that LMWHs may be applied at home safely for a prolonged period of time, for example 45 days (45). Personal experience of the author reaches 4 months. While standard heparin enhances platelets aggregation, LMWHs seem not to do so (22). Also, side effects like thrombocytopenia and osteoporosis seem to be less frequently recorded with LMWHs. Basic insufficiencies of LMWHs are shorter period of clinical expe-

rience and higher market prices (but home administration and less need for laboratory control causes net cost savings for LMWH (46). Comparative trials had shown similar or better attributes of LMWH vs standard heparin in general, as well as in UAP / non-Q AMI (15, 45-49). Our first results have been encouraging, due to maximal efforts to control both heart rate (mainly by beta blockers and carvedilol, amiodarone, etc.) and blood pressure (ACE inhibitors, nitrates, etc.). Also, chance may play a role in such small study, and even selection bias. Absence of heparin rebound is identical to TIMI 11 A results with LMWH (31), as well as other authors experiences (36).

Cannon (50), suggests that direct thrombin inhibitors (like hirudin) have more predictable response than standard heparin and decrease reocclusions. It is of practical importance in pts with high risk for thrombosis to ensure correct heparin-warfarin overlap (if we intend to proceed with oral anticoagulant therapy): standard heparin should be not be abandoned until INR (marker of warfarin efficacy) is at least 2–3 in two consecutive days. Otherwise, warfarin may promote thrombosis (51), (due to protein C decrease). Thus, heparin should be continued for 2–3 days after achieving therapeutic INR (usually not before 4–5 days), to be sure that not only F VII (responsible for aPTT) has fallen, but others also, especially prothrombin!

Of practical importance, there has been possible ways to avoid heparin rebound, with logic rationale and confirmation in a few trials so far: longer LMWH treatment. Namely, in UAP and AMI increased risk for cardiac events lasts for at least 1.5–3 months after acute episode (4,52–56). Visible residual thrombus was seen in 77% by coronary angiography up to 1 month after coronary event (56). Thus, short-term therapy for a long term thrombogenic surface or diseased artery is insufficient (30). Prevention should be prolonged (45), at least in high risk pts. Minimum duration of more potent antithrombotic therapy appears to be 30 days, during which time most events are clustered (30). Standard heparin Th lasts usually only a few days (partially because pts can not tolerate continuous iv infusions, preferred in cardiology, for many days).

LMWHs can be given at home (31), do not require

aPTT monitoring and have predictable effect (46,57,58). After acute coronary event longer treatment with LMWH added to aspirin was suggested (45,59-61), in order to diminish risk for AMI / sudden cardiac death. FRISC study authors (47) recommend that high risk UAP / non-q AMI should continue with LMWHs until coronarography and revascularisation. High risk may be confirmed with cardiac troponin T finding in the blood (> 0.1 micro g/L) (62). Very similar view to ours was published by Glick et al. (36) LMWH (Clexan) was given following standard heparin from day 5th–30th after AMI in pts who received streptokinase. In comparison with group without LMWH in therapy, there was re-AMI number decreased, as well as the number of total cardiac events after 6 months. The before mentioned study was well designed and exclusion criteria were not only contraindications for heparin but also comorbid factors, capable of enhancing mortality, but uninfluenced by heparin.

Conclusions

1) With heparin treatment *in any medical branch*, heparin rebound phenomenon should be *always* looked for, which promotes rethrombosis and makes prognosis worse.

2) Prevalence of heparin rebound can be lowered probably with adequate duration, dose and proper stepwise discontinuation of standard heparin and LMWH, together with other suggested actions to decrease coagulation and platelets activation.

3) Our initial very encouraging experience confirms literature data suggesting low incidence of heparin rebound phenomenon with enough long LMWH usage. LMWH applied for a few weeks seems justified in pts at high risk for rethrombosis.

4) After qualified and very careful risk / benefit evaluation of individual patient, LMWHs may be given easily, with low bleeding rates (having gastric protection provided), and without a need for aPTT monitoring.

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FENOMEN "USKRAĆIVANJA" HEPARINA U AKUTNIM KORONARNIM SINDROMIMA: PREDNOST NISKOMOLEKULSKOG HEPARINA

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Kratak sadržaj: Fenomen "uskraćivanja" ("rebound") je tako nazvan da ilustruje APNS reaktivaciju nakon prestanka primene heparina. Opisano je grupisanje reinfarkta i oštar porast stvaranja i delovanja trombina u prvim časovima nakon obustave heparina (nakon trombolize), što se delimično pripisuje heparin "rebound" efektu.

Cilj studije je bio da ukaže na značaj malo poznatog problema uskraćivanja heparina, da sugeriše moguće puteve za njegovo izbegavanje i da prikaže sopstvene početne rezultate sa niskomolekulskim heparinom nadroparinom u tom kontekstu, jer podaci o tim temama kompletno nedostaju u našoj literaturi. Ukupni broj analizovanih pacijenata bio je 45 (27 muškaraca, 18 žena), prosečne starosti $59,4 \pm 4,3$ g, a svi su primali H₂ blokator u cilju zaštite želuca.

Preciznim praćenjem nije nadjen heparin "rebound" fenomen, što može biti povezano sa dužinom terapije. Uz pažljivu kontrolu srčane frekvence i krvnog pritiska tokom hospitalnog praćenja, adekvatna antitrombinska terapija izgleda da je poboljšala njihovu prognozu. Neželjeni efekti bili su minorne hemoragije: u 5 bolesnika ekhimoze na mestu uboda injekcije u jednog gingivalna hemoragija, dok 39 pacijenata nije imalo krvarenje, uključujući devet sa anamnezom ulkusa. Ima praktičnih sugestija da se smanji fenomen uskraćivanja heparina: 1) da se smanje protrombotske tendencije u krvi, nevezane za heparin; 2) da se popravi terapija standardnim heparinom i 3) da se koriste noviji antitrombotski lekovi.

Zaključujemo: Prevalenca fenomena "uskraćivanja" heparina verovatno se može smanjiti adekvatnim trajanjem i dozom standardnog i niskomolekulskog heparina, uz druge sugestije da se redukuje aktivacija koagulacije i aktivacije

trombocita. Literaturni i sopstveni podaci ukazuju na malu incidencu heparin rebound fenomena sa dovoljno dugom primenom niskomolekulskih heparina. Oni se mogu lako davati, uz mali procenat krvarenja, a bez potrebe za aPTT monitoring. Znači, višenedeljna terapija niskomolekulskim heparinom izgleda da je opravdana u pacijenata koji su na visokom riziku za retrombozu.

Ključne reči: Niskomolekulski heparin, heparin, rebound, akutni infarkt miokarda, nestabilna angina

Received: February 12, 1999