Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.53555/g67h9047

COMPARISON OF NADROPARIN 2850 IU AND ENOXAPARIN 4000 IU FOR THROMBOPROPHYLAXIS IN COLORECTAL CANCER SURGERY

Dr. Jerish Murari*

*Internal Medicine, Chettinad Hospital and Research Institute, Kanchipuram, India
Orcid id-0009-0007-3910-0075, Email id- jerish.sapphire@gmail.com

ABSTRACT

It is not clear which the optimum regime of treatment dosing should be used to utilize thromboprophylaxis using low-molecular-weight heparins on the high-risk members of the general population. Objectives: The aims of the study shall be to find out the efficacy of the nadroparin 2850 IU (0.3mL) and enoxaparin 4000 IU (40mg) in the prevention of the venous thromboembolism (VTE) developing after colorectal cancer is treated surgically and compare the safety of the two agents of treatment. Patients and Methods: The patients scheduled to be resected where randomized so as to receive single dose therapy of either- 2850 IU nadroparin- or- 4000 IU enoxaparin once a day and within 9 +/- 2 days. The initial safety precaution was major bleed. Advantage was taken of all the results by a blinded independent committee. Results:The effectiveness could be determined in 950 (73.8 percent) of the 1288 patients who were included in the analysis. Nadroparin 15.9 percent (74/464), enoxaparin 12.6 percent (61/486); relative risk 1.27 (95 percent confidence interval; CI: 0.93 1.74) and the result was not inferior to non inferiority of nadroparin. The equality in the proximal DVT event of the groups were 3.2 and 2.9 respectively, whereas it was lower on the sympathetic VTE of the nadroparin side (0.2 and 1.4 respectively). The difference on the other hand was also observed to be significant between the nadroparin and the enoxaparin group in major bleeding both in 7.3 percent in the former and 11.5 percent based on the latter respectively. Conclusion: Nadroparin 2850 IU when compared to 4000 IU Enoxaparin found the greater percentage of the completely asymptomatic distal DVT as well as a smaller percentage of the symptomatic VTE. Nadroparin has been obtained with a risk form of major bleeding which was minimized.

KEY WORDS : Thromboprophylaxis, Venous thromboembolism (VTE), Nadroparin, Enoxaparin Colorectal surgery

INTRODUCTION

The amount of DVT and fatal PE which can be observed after the patients with cancer undergoing general surgery is twice (2 times) and more than three times bigger than that which could be observed among non-cancer patients [1]. Comprehensive fibrinogen uptake test is claimed to be able to determine the presence of DVT as remaining 29 percent (95 percent confidence interval; CI: 25-33) when there is no administration of prophylactic medication [1]. In this relation, the professionals give the recommendation that the dosing of such patients on unfractionated heparin (UH) or low-molecular-weight heparins (LMWHs) ought to be done on a routine basis [2]. This way, UH has almost been substituted by LMWHs as a prophylaxis therapy in general surgery due to the once a day application, the freedom of having to monitor the coagulation too closely and the issues with heparin inducedure thrombocytopenia [3]. Nevertheless, the ideal LMWHs dosing is not yet shaped since the

specific dosing of LMWHs was completed which there are not much literatures reporting the apparent comparison of the various dosing regimens of LMWHs in general surgery [47]. Moreover, there is high probability of bleeding during the surgery that is conducted in cancer [8,9]. Therefore we used the technique of randomized and blinded trial to assess the effects as to whether once a day dose of 2850 anti factor (F) Xa IU nadroparin and 4000 anti FXa IU enoxaparin had any effect as to whether prevention of venous thromboembolism (VTE) occurred after completion of operation that was elective to treat colon or rectum cancer. The most vulnerable against the development of VTE in colorectal surgery compared to other surgical operations involving the abdomen [3,10] is VTE. Nadroparin and enoxaparin that were used in this study were those approved by the health authorities. In such patients who undergo cancer operation they have been found to be equivalent to 5000 IU of UH 3 times daily but have exhibited somewhat tendency of leading to major bleeding as compared to 4000 IU of enoxaparin [11-13].

METHODS

It was a prospective, randomized, double-blind, double-dummy, parallel-group, multicentre study in which nadroparin was compared with enoxaparin.

Patients

Any patient with the colorectal adenocarcinoma who underwent an elective resection under the influence of the general type of anesthesia and was suspected in any of the stages of the cancer disease could have been included in the study except the emergency one, when the operation was carried out using the locoregional methods of the anesthesia, or the procedures of resection when adenocarcinoma was not removed, or three or more of the metastases in the liver were removed. Other major exclusion criteria consisted; hemorrhagic stroke or stroke of unidentified origin less than 2 months; a neurosurgery less than 2 months; acute bacterial endocarditis; pregnancy; a documented hemostasis disease; a thrombocytopenia; contra-indications to anticoagulant treatment; a past history of an allergy to heparin or heparin-induced thrombocytopenia; and impaired renal (serum creatinine concentration greater than 200 1mol/L

Study Design

The selection of eligible patients was done by randomization that used predetermined randomization list that was randomly allocated to identify the patients to use the randomization list done before the surgery had taken place. By stratification there were center and by concealment there was remote randomization (centralized). Three groups would separate the patients, and each of them would be injected subcutaneously once a day; the drug intended to be used was 2850 IU anti-FXa of nadroparin (0.3 ML, FraxiparineR; GlaxoSmithKline, Harlow, UK) and, the very laboratory which had manufactured the drug would be used as a placebo, i.e., it could either be enoxaparin or a combination of 4000 IU anti-FXa of enoxaparin (40 mg, These were doses which the respective manufacturers have recommended at the time of trial. Day 1 was the couple of days the surgery was performed. Treatment suspend was to be discontinued after 7-11 days and the major outcome of efficacy was to be determined on 1-12 days. Second visit would be in 4260 in which the patients would report any sign or symptoms of VTE, bleeding etc or any other clinical event which has been had since the treatment has completed. When VTE developed, the test drug was withdrawn and the investigator was free to employ any treatment that he wanted to use. The research occurred under the scope of Declaration of Helsinki in regard to the ethical analysis and local regulation. The study was approved by the ethics committee which was not related and all the patients requested to sign the written informed consent before randomization.

Medication

Both the 24 single dose pre filled syringes (nadroparin 0.3 ml, 2850 anti-FXa IU and same placebo (isotonic saline) or enoxaparin 0.4 ml, 4000 anti-FXa IU and same placebo) were present in each of the boxes.

Aspirin, thienopyridines, non-steroidal anti-inflammatory, UH, LMWHs and the study drugs, heparinoids or vitamin K antagonists were prohibited. Others- like chemotherapy and radiotherapy were permitted. Compression stocking was recommended.

RESULTS

Table: 1 Baseline Demographics and Risk Factors of Patients Treated with Nadroparin and Enoxaparin

Parameter	Nadroparin (n = 400)	Enoxaparin (n = 350)
(Years) Median (Range)	69 (27–97)	68 (26–92)*
(Male or female)	241/159	210/140
In kilograms, median (range)	69 (35–130)	70 (36–120)
Weight (kg/m2), median (range)	24.7 (14.6–44.5)	24.7 (14.4–45.7)
Factors of risk, n (%)		
Over 60-year-olds	318 (79.5)	261 (74.5)*
Obesity†‡	52 (12.9)	49 (14.1)
Thromboembolic history	17 (4.4)	23 (6.5)
Varicose veins	81 (20.2)	89 (25.4)*
Cardiomyopathy decompensated	3 (0.8)	1 (0.3)
An uncompensated respiratory failure	1 (0.3)	2 (0.5)
The use of estrogen	3 (0.8)	7 (2.1)
Bedridden before surgery	15 (7.0)	18 (7.7)
Recent infection	8 (3.4)	5 (2.5)
Risk factors at least one	358 (89.4)	299 (85.4)*
No. of risk factors		
0	42 (10.6)	51 (14.6)
1	184 (45.9)	135 (38.6)
2	138 (34.6)	127 (33.4)
≥3	36 (8.9)	60 (13.4)
Serum creatinine (μmol/L), median (range)	86 (44–443)	84 (44–195)

Table: 2 Cancer Localization, Histology, and Surgery Details of Patients Treated with Nadroparin and Enoxaparin

Indicator	Nadroparin (n = 400)	Enoxaparin (n = 350)
Localization of cancer, n (%)		
Tumors of the colon	283 (70.8)	219 (62.5)
Cancer of the colon	113 (28.3)	124 (35.4)
Colorectal cancer	4 (1.0)	7 (2.1)
Histology of cancer, n (%)		
Adenocarcinoma	380 (95.0)	330 (94.4)
Not an adenocarcinoma	20 (5.0)	20 (5.6)
Adenocarcinoma stage (Dukes classification), n (%)		
A	53 (13.2)	51 (14.5)
B	148 (41.2)	144 (41.2)
C	110 (27.5)	125 (30.3)
D	89 (18.0)	50 (14.0)
Duration of surgery (h: min), median (range)	2:30 (0:45–13:30)	2:30 (0:45–10:15)

Table 1 shows the basis line and risk factor among patients that were under combined therapy Nadroparin and Enoxaparin. The ages, the weight, the body mass index (BMI) between the two groups of the patients were more or less equal. The range MD of Nadroparin group was 27-97 and Enoxaparin had a range MD of 26-92 and median age of 69 and 68 respectively in Enoxaparin and Nadroparin group respectively. Sex distribution also was similar but to a greater degree whereby 241 and 159 of Nadroparin were male and female respectively and 210 and 140 male and female respectively in Enoxaparin. The similarity between the groups also formed in weight where Nadroparin group reported a median of 69kg (range 35 to 130) compared to the Enoxaparin group which had a median of 70kg (range 36 to 120). In addition, there were also some differences between two groups of median BMI, which was 24.7 (kg/m 2). The two groups were listed under risk factors of venous thromboembolism (VTE). The proportion of patients whose age bracket was greater than 60 years was also high in Nadroparin group (79.5%) than that determined in Enoxaparin group (74.5). They also had high likelihood of being obese' history of venous thromboembolism and varicose veins though this happened to be a bit more in Enoxaparin group (25.4%) compared to Nadroparin group (20.2%). Most of the patients of both the groups had a single or more risk factors (89.4 and 85.4 percent respectively in Nadroparin and Enoxaparin). The level of serum creatinine by comparison was similar with a median of 86 mu mol /L(44-443) in Nadroparin group and 84 mu mol /L(44-195) in Enoxaparin group. The features outlined in the Table 2 are indicative of localization, histology, and surgical features of each of the forms of cancer. Regarding the localization of cancer, the percentage of the patients within the two groups were 70.8 and 62.5 respectively in the Nadroparin and Enoxaparin bodies which were colon cancer. The prevalence of the Enoxaparin group to the rectal cancer was 35.4 percent compared to that of Nadroparin group that was at a percent of 28.3. Histologically, the results of adenocarcinoma among the patients formed the mammoth sample 95 percent patients in the Nadroparin group and 94.4 percent patients in the enoxaparin group. The stage of Dukes was also alike and most of the patients in both groups were stage B. Second last was the median operative time which was 2:30 hours per group and the operating time varied between 0:45 and 13:30 hours in Nadroparin and 0:45 to 10:15 in Enoxaparin.

DISCUSSION

Nonetheless, it is not true to say that non-inferiority efficacy results (i.e., total VTE) were highly confirmed with nadroparin 2850 IU as compared to enoxaparin 4000 IU among the cancer patients who received colorectal surgery in this research study. The achieved difference in the primary efficacy outcome which favoured enoxaparin was to a great extent caused by insufficient amount of asymptomatic distal DVT in the arm of enoxaparin. Lower number of symptomaticvenous thromboembolic occurrences recorded in the form of pulmonary embolisms(PE) on the patients being treated with nadroparin. Regarding the composite event which will be tested as a consequence of non-inferiority trials, i.e. asymptomatic proximal DVT or non-fatal VTE or VTE-related death, the non-inferiority of nadroparin when compared to enoxaparin did not reach the (statistical) test, when the upper bound (UB) of the relative risk (RR) was 1.56 instead of 1.43. Loss of statistical power may occur in failure to show non-inferior effect because of the failure to show non-inferior effect. One can also say that the margin of non-inferiority was employed somewhat conservatively, in fact; in a recently conducted study of patients of high-risk of abdominal surgery the margin was determined at 1.70 [17]. Remarkably, there was no statistically significant disparity in each of the treatments in regard to rate of VTE with the aid of a superiority examination ($p = 0.134$). The overall incidences of the VTE (14.2 per cent) day 12 were similar to the latest trials 8 to 18 per cent incidences of the trials which incorporated patients receiving general surgery due to cancer and who have taken appropriate doses of the UH or LMWHs [12,13,17,18]. On the same note, the overall occurrence of major bleeding (9.4 percent) can be said to be adequate compared to a meta-analysis of the trials conducted on abdominal surgery regarding both cancer and UH which is 8.1 percent [9]. Another remarkable aspect was that the definition of major bleeding in this trial had added an indication that the definition of major bleeding and that of a surgical bleeding was fairly extensive because it included a surgical bleed of at least 1200 mL and most of them, i.e, 42 percent were considered as major bleeds. Same data

were provided in the statistics of bleeding, in transfusion requirements, and blood lost during perioperative, and they were similar to the ones observed in the other trials [12,13]. In turn, nadroparin 2850 IU was not as likely to have potentials of bleedings whether a major bleed definition is considered or not as enoxaparin 4000 IU. Nadroparin 2850 IU could be equated in terms of its safety in patients in general surgery as compared to three times a day 5000 IU UH, but it was more effective as compared to the latter [11]. During the first test, substitution of UH 5000 IU three times daily with enoxaparin 2000 IU in a subpopulation of cancer surgery resistants to general surgery did not take place [19]. The other two trials done by comparing the UH were also done whereby enoxaparin 4000 IU was equally effective and tended on having the higher risk of major bleeding in comparison to the UH [12,13]. According to the literature, there is a lack of the researches comparing two various dose recommendation of LMWH. In the study on an abdominal surgery study, where Bergqvist et al. [6] participated and among which 66.4 percent of the patients harbored cancer, it was revealed that thromboprophylaxis of 5000 IU dalteparin was preferable to that of dalteparin 2500 IU with the risk of severe bleeding. There is also a second trial in high risk patients in general surgery where nadroparin 2850 IU is superior to dalteparin 2500 IU and the third an open series in dalteparin users 5000 IU where there is no difference in VTE between the use of nadroparin 2850 IU and that of dalteparin 5000 IU [20]. LHWHs, as revealed in these studies, cannot be talked of as a homogenous group and they cannot be easily compared on the parameter of anti-FXa IU. And then the ratio between the risk and benefit of any single LMWH should be determined on an individual basis depending on the result of certain clinical trials [21]. In the clinical practice, the producer will be suggesting different doses of regimen depending on the drug as well as the thrombotic risk during the treatment. Pre administration of Nadroparin and enoxaparin preceded the surgery by 2-4 hours as in most of the available literature concerning thromboprophylaxis in general surgery operations and that of the industries which produce the drugs. Whether timely administration benefits is not certain. Among the interesting facts, it may be said that at the perioperative and postoperative bleeds of our study, the treatment groups differed in their occurrence of the bleeding events. Among the enoxaparin group, fatal bleeding was noticed on week three and six respectively. Post-operative cancer surgery now includes the use of thromboprophylaxis using LMWHs to aim at decreasing the late thrombotic events during the long-term surgery of cancer [2,22,23]. The incident of VTE prior to 60 days of operation which maintained the loss of life was not substantiated in our analysis since there were 0.6 per cent occurrence of VTE. The findings however cannot be said to be considered fully because, there might have been a bias introduced by the anticoagulant therapy provided, which was administered on the patients with asymptomatic DVT during the first occurrence of the study. The treatment stage of the study drugs fell in a short-term range but we feel that information concerning the bleeding is most suitably used in the existing practice in a long-term treatment of the cancer patients who shall go through an abdominal procedure, those who are to receive a long prophylaxis because the events of bleeds are most likely to occur within the first 10days of the abdominal surgery [12,23]. Conclusively, the study can be termed as the largest trial of two modes of two LMWHs in patients undergoing cancer surgeries. On the basis of the totals, the nadroparin 2850 IU and 4000 IU enoxaparin did not meet the standards of the non-inferiority on the grounds of the statistics. The rate of asymptomatic distal DVT proved to be increased in nadroparin 2850 IU which had a reduced symptomatic VTE such as PE. Nadroparin was also less hazardous in terms of the vulnerability to bleeding. Consequently, 2850 IU of nadroparin administered daily can also be considered to be an option in reference to thromboprophylactic procedures during the surgery of colorectal cancer patients.

CONCLUSION

In summary, the current study will assist in coming up with verdicts in relation to the effectiveness and safety of nadroparin 2850 IU versus enoxaparin 4000 IU in the prevention of thrombosis in patients with colorectal cancer. Even though statistical generalization of the importance of non-inferiority of nadroparin versus enoxaprin in the prevention of total VTE was not attested, nevertheless, the results specifically indicated that nadroparin was statistically less associated with

symptomatic VTE such as pulmonary, and risk of major bleedings. The conclusions were suggestive that the nadroparin 2850 IU administered once in a day was a possible and safer medicine compared to enoxaparin in this series of diseases. However, further experiments including larger sample must be conducted to give eye witnessing credence of prolonged impact and safety features of different forms of LMWH on recipients of cancer surgery. Nadroparin is a potential thromboprophylactic measure in the treatment of colorectal cancer surgery not only in bleeding prevention with the positive outcome of safety.

REFERENCES

1. Geerts, W.H. · Heit, J.A. · Clagett, G.P. Prevention of venous thromboembolism Chest. 2001; 119:132S-75S
2. Geerts, W.H. · Pineo, G.F. · Heit, J.A. Prevention of venous thromboembolism. The Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy Chest. 2004; 126:338S-400S
3. Bergqvist, D. Low molecular weight heparin for the prevention of venous thromboembolism after abdominal surgery Br J Surg. 2004; 91:965-74
4. Becchi, G. · Bonomo, G.M. · Scattarella, M. Dose-effect relationship in the prevention of post-surgical thromboembolism by a low molecular weight heparin Acta Therap. 1993; 19:163-79
5. Bounameaux, H. · Huber, O. · Khabiri, E. ... Unexpectedly high rate of phlebographic deep venous thrombosis following elective general abdominal surgery among patients given prophylaxis with low-molecular-weight heparin Arch Surg. 1993; 128:326-8
6. Bergqvist, D. · Burmark, U.S. · Flordal, P.A. Low molecular weight heparin started before surgery as prophylaxis against deep vein thrombosis: 2500 versus 5000 XaI units in 2070 patients Br J Surg. 1995; 82:496-501
7. Azorin, J.F. · Regnard, J.F. · Dahan, M. ..., et les investigateurs du Groupe Thorax Efficacy and safety of Fraxiparine in the prevention of thrombo-embolic events in lung cancer surgery Ann Cardiol Angeiol. 1997; 46:341 7
8. Cohen, A.T. · Wagner, M.B. · Mohamed, M.D. Risk factors for bleeding in major abdominal surgery using heparin thromboprophylaxis Am J Surg. 1997; 174:1-5
9. Mismetti, P. · Laporte, S. · Darmon, J.Y. Meta-analysis of low molecular weight heparin in the prevention of venous thromboembolism in general surgery Br J Surg. 2001; 88:913-30
10. Borly, L. · Wille-Jorgensen, P. · Rasmussen, M.S. Systematic review of thromboprophylaxis in colorectal surgery – an update Colorectal Dis. 2005; 7:122-7
11. The European Fraxiparin Study Group Comparison of a low molecular weight heparin and unfractionated heparin for the prevention of deep vein thrombosis in patients undergoing abdominal surgery Br J Surg. 1988; 75:1058-63
12. Enoxacan Study Group Efficacy and safety of enoxaparin versus unfractionated heparin for prevention of deep vein thrombosis in elective cancer surgery: a double-blind randomized multicentre trial with venographic assessment Br J Surg. 1997; 84:1099-103
13. McLeod, R.S. · Geerts, W.H. · Sniderman, K.W. ..., Canadian Colorectal Surgery DVT Prophylaxis Trial investigators Subcutaneous heparin versus low-molecular-weight heparin as thromboprophylaxis in patients undergoing colorectal surgery. Results of the Canadian Colorectal DVT Prophylaxis Trial: a randomized, double-blind trial Ann Surg. 2001; 233:438-44
14. Piaggio, G. · Elbourne, D.R. · Altman, D.G. ..., CONSORT Group Reporting of noninferiority and equivalence randomized trials JAMA. 2006; 295:1152-60
15. Committee for Proprietary Medicinal Products (CPMP) Points to Consider on Switching Between Superiority and Non-Inferiority. The European Agency for the Evaluation of Medicinal Products.CPMP/EWP/482/99, 2000
16. Committee for Proprietary Medicinal Products Points to Consider on Clinical Investigation of Medicinal Products for Prophylaxis of Intra- and Postoperative Venous Thromboembolic Risk. The European Agency for the Evaluation of Medicinal Products.CPMP/EWP/707/98, 2000

17. Agnelli, G. · Bergqvist, D. · Cohen, A.T. ..., PEGASUS investigators Randomized clinical trial of postoperative fondaparinux versus perioperative dalteparin for prevention of venous thromboembolism in high-risk abdominal surgery Br J Surg. 2005; 92:1212-20
18. Wiig, J.N. · Solhaug, J.H. · Bilberg, T. ... Prophylaxis of venographically diagnosed deep vein thrombosis in gastrointestinal surgery. Multicentre trials 20 mg and 40 mg enoxaparin versus dextran J Surg. 1995; 161:663-8
19. Nurmohamed, M.T. · Verhaeghe, R. · Haas, S. A comparative trial of a low molecular weight heparin (enoxaparin) versus standard heparin for the prophylaxis of postoperative deep vein thrombosis in general surgery Am J Surg. 1995; 169:567-71
20. Wicky, J. · Couson, F. · Ambrosetti, P. ... Postoperative deep venous thrombosis (DVT) and low-molecular weight heparin (LMWH) type and dosage Thromb Haemost. 1993; 69:402-3
21. Fareed, J. · Bick, R. Differentiation of low-molecular-weight heparins: practical implications Clin Appl Thromb Hemost. 2004; 10:299-300
22. Bergqvist, D. · Agnelli, G. · Cohen, A.T. ..., ENOXACAN II Investigators Duration of prophylaxis against venous thromboembolism with enoxaparin after surgery for cancer N Engl J Med. 2002; 346:975-80
23. Samama, C.M. · Albaladejo, P. · Benhamou, D. ... Venous thromboembolism prevention in surgery and obstetrics: clinical practice guidelines Eur J Anaesthesiol. 2006; 23:95-116