Orthopedic & Muscular System: Current Research

Lunzer, et al., Orthop Muscul Syst 2015, 4:1
DOI: 10.4172/2161-0533.1000185

Research Article Open Access

A Prospective, Active-control, Non-inferiority Study of the Effectiveness of Low Molecular Weight Heparin in the Prophylaxis of Postoperative Thrombotic Events in Patients Undergoing Spinal Surgery

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Abstract

Background: The Incidence of verified thrombotic events after elective spine surgery is 18%. Low-Molecular-Weight-Heparin (LMWH) is routinely given on the day before surgery. A postoperative start of the thrombotic prophylaxis could be an advantage in cases with opening of the spinal canal and for preventing epidural bleeding.

Patient and methods: This active-controlled non-inferiority trial compared the effectiveness and safety of LMWH started pre- or postoperatively in patients undergoing spinal surgery. We analysed the incidence of clinically symptomatic venous thromboembolism.

Results: A total number of 241 patients were followed over 14.6 patient-years. The incidence risk of fatal thromboembolisms was 0.011 (95%CI 0.0003 to 0.06) for the group with preoperative treatment and 0.01 (95% CI 0.0002 to 0.04) for the postoperatively treated group. The crude risk ratio was 1.65 (95%CI 0.10 to 26.03).

There was no statistically significant difference in risk across groups (p=0.72). The Poisson regression model including follow-up time showed an incidence rate ratio of 0.67 (95% 0.04 to 10.74, p=0.779). There was no increased risk for complications (p=0.211).

Conclusion: This study demonstrates that the postoperative start of LMWH in the prophylaxis of thrombotic events in patients undergoing spinal surgery does not affect safety or the incidence of complications.

Keywords: Thrombotic prophylaxis; LMWH; Epidural bleeding; Thromboembolism

Introduction

Postoperative venous thromboembolism, especially after arthroplasties of the hip or the knee, is one of the most feared complications in elective orthopaedic surgery. There are only few reports of postoperative thrombotic events after spinal surgery [1]. In current studies it is estimated that without anticoagulant therapy rates of deep vein thrombosis are nearly as high as 50% [2,3]. Studies including clinically asymptomatic patients after elective operations of the spine showed phlebograhpically verified thrombotic events in 18% of all patients [4].

To prevent such tragic outcomes low molecular weight heparins (LMWH) are broadly used in Europe, while warfarin is preferred in the USA [3,5,6], However, heparin, as well as warfarin, is often associated with major bleedings, requires complex dose adjustment and monitoring. LMWH is safer and has fewer side effects due to its preferable anti-Xa to anti-IIa activity. Currently, there is a variety of different LMWH products on the market. Bemiparin is a derivate with an anti-Xa:anti-IIa ratio of 8 and a half-life of more than 5 hours [7,8]. The clinical potency has already been verified in numerous studies [9,10].

Beside the obvious risk of operation, other factors for developing an thrombotic event, such as advanced age, malignant diseases, prolonged operations, pre- or postoperative reduced mobility and a patient history of thrombotic events have been identified and should be addressed [11,12]. Even in obese patients, LMWH was shown to be effective and safe after orthopaedic operations, without the need to adapt the dose [2]. An evidence-based guideline, published by the North American Spine Society, included level IV evidence that LMWH can be given safely on the day before routine, elective surgery [13].

There is concern about the use of anticoagulants in spinal surgery because of bleedings, postoperative haematomas and even neurologic defects due to them [14].

A postoperative start of the thrombotic prophylaxis could be an advantage in cases with opening of the spinal canal and for preventing epidural bleeding, if the prophylactic effectiveness would not be affected. Therefore we conducted a controlled cohort study of 241 patients undergoing elective spine surgery to prove the effectiveness and safety of LMWH prophylaxis even when it is started postoperatively.

Patients and Methods

This study was designed as an active-controlled non-inferiority trial to assess the effectiveness and safety of thromboembolic prophylaxis with Bemiparin Sodium treatment started pre- or postoperatively in patients undergoing opening the spinal canal [15]. Furthermore, we searched for correlations between secondary diagnoses and a thrombotic event or any kind of complication. Preliminary we sought approval from local ethic committee (EK 1507/2012). All patients

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Received January 26, 2015; **Accepted** February 16, 2015; **Published** February 23, 2015

Citation: Lunzer A, Vavken P, Grohs JG (2015) A Prospective, Active-control, Non-inferiority Study of the Effectiveness of Low Molecular Weight Heparin in the Prophylaxis of Postoperative Thrombotic Events in Patients Undergoing Spinal Surgery. Orthop Muscul Syst 4: 185. doi: 10.4172/2161-0533.1000185

accepted that the aggregated personal information would be used for research.

All included patients were treated at the Department of Orthopaedic Surgery at the Medical University of Vienna–a tertiary referral centre for orthopaedic surgery. Every patient undergoing spine surgery from Nov 2008 to Nov 2009 was included in the study group. The control group of 91 patients was randomly selected out of a cohort study, which took place between 2006 and 2008. The patients were undergoing elective orthopaedic surgery on the spine and had to fulfil the same selection criteria as the current study group. Two thirds of all the included patients were undergoing a major procedure, such as 360-degree fusion of the spine. Patients with a history of thrombo-embolic diseases, haemophilia, or any contraindication for anticoagulation with LMWH were excluded from our study (Figure 1).

All patients were given one dosage Bemiparin Sodium 3500 IU/day subcutaneously. The patients of the study group received the first dosage in the evening after the operation, while those of the control group were given the first dosage in the evening before the operation.

Two blinded investigators assessed outcomes independently. All clinically symptomatic thrombotic events were specified as primary endpoints of the study. In all cases, where a thrombotic event was suspected, a D-dimer testing followed by Duplex Doppler ultrasound imaging was conducted. Major bleeding and delayed wound healing requiring surgical intervention were specified as secondary endpoint. All patients were assessed twice daily during their hospital stay and weekly after discharge. Patients with major procedures such as 360-degree fusions of the spine were followed for a minimum of 28 days, patients undergoing minor procedures as spinal decompression or microdiscectomy for 21 days. General anaesthesia was administered during all surgical procedures (Table 1).

Statistical evaluation

Statistically evaluation was done as described previously [2]. Briefly, after descriptive analysis of the data set, a raw risk ratio was calculated. To account for different follow-up times, all data was introduced into a Poisson regression model. Age and gender were considered as covariates to account for potential confounding [3]. To compare the effectiveness and safety of the two treatment arms an active-controlled non-inferiority design was chosen [4]. Following the current FDA recommendation the non-inferiority margin (δ) was defined using the "95-95 method" [5-7]. Briefly, historical, level-I data on the relative effectiveness of the control group (preoperative administration of bemiparin) versus placebo was obtained from published meta-analyses [8,9]. One half of the worst limit of the CI of this effect was used as δ, i.e. 0.08 for DVT and 0.19 for wound healing complications. All results are given as means with 95% confidence intervals (95%CI) [10]. All calculations were done using intercooled Stata 10 (CollegeStation, Tx). An alpha of 5% was considered significant.

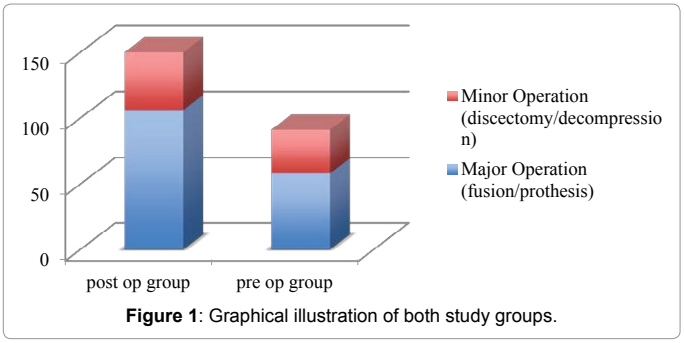

Figure 1: Graphical illustration of both study groups.

Treatment groups			
Variable	**pre op**	**post op**	**p-value**
patients	n=91	n=150	
age	56.5 ± 13	56.9 ± 15.8	p=0.8397
Sex distribution*	54 m/37 f	60 m / 90 f	p=0.0037
Hospital follow up time*	3.7 ± 2.1 weeks	3.0 ± 1.2 weeks	p=0.2572

* given as mean ± SD

Table 1: Demographics of the two treatment groups; there is a statistical significant difference in sex distribution, but clinically this difference is negligible.

Results

A total number of 241 patients were followed over 14.6 patient-years. Among these, 91 (54 male, 37 female) aged 56.5 ± 13 years received anticoagulative treatment preoperatively and were followed for 3.7 ± 2.1 weeks, adding up to 5.9 patient-years total follow-up. 150 patients (60 male, 90 female) aged 56.9 ± 15.8 years received treatment postoperatively and were followed for 3.0 ± 1.2 weeks or a total of 8.7 patient-years. These data are consistent with no significant difference in mean age (p=0.8397) or in follow-up time (p=0.2572), but a significant difference in sex distribution (p=0.0037). Hence gender was included as a potential confounder in the multivariate regression, but age was not.

The incidence risk of fatal thromboembolisms was 0.011 (95%CI 0.0003 to 0.06) for the group with preoperative treatment and 0.01 (95% CI 0.0002 to 0.04) for the postoperatively treated group. Thus the crude risk ratio was 1.65 (95%CI 0.10 to 26.03), which is consistent with no statistically significant difference in risk across groups (p=0.72). The Poisson regression model including follow-up time showed an incidence rate ratio of 0.67 (95% 0.04 to 10.74, p=0.779). Introduction of gender as potential confounders led to an attenuation of this IRR to 0.17 (95%CI 0.007 to 4.03). Again, this was consistent with a non-significant difference (p=0.272).

The incidence risk of complications (Figure 2) was 0.08 (95%CI 0.02 to 0.13) for the group with preoperatively and 0.04 (95%CI 0.01 to 0.07) for the group with postoperatively begun treatment, producing a crude risk ratio of 0.51 (95%CI 0.18 to 1.48), which is, again, not statistically significant (p=0.211). The Poisson model showed a crude rate ratio of 0.57 (95%CI 0.19 to 1.7, p=0.314) and 0.62 (95%CI 0.21 to 1.86. p=0.393) after adjustment for age and gender (Table 2).

The non-inferiority assessment showed equivalent effectiveness between both treatment arms with a δ of 0.08 well within the CI of both the crude and adjusted the risk ratios. For postoperative complications,

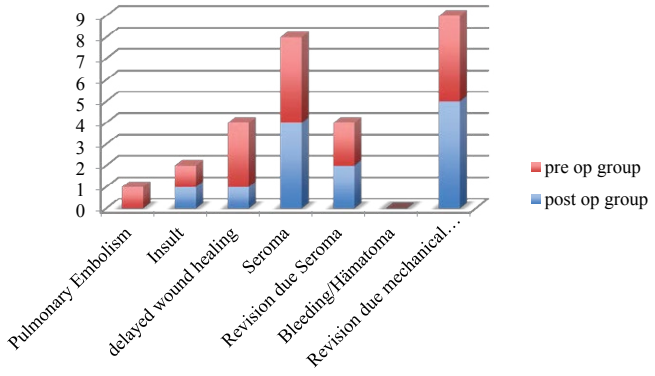

Figure 2: Complcations in both study groups.

	Group		
Complications	**pre op**	**post op**	**p-value**
Incidence Risk	0.08 (95%CI 0.02 to 0.13)	0.04 (95%CI 0.01 to 0.07)	
Crude Risk Ratio	0.51 (95%CI 0.18 to 1.48)		p=0.211
Adjusted for age	0.57 (95%CI 0.19 to 1.7)		p=0.314
Adjusted for gender	0.62 (95%CI 0.21 to 1.86)		p=0.393

Table 2: Incidence risk of complications and crude risk ratio in the Poisson model were in both groups not significant; even adjusted to covariates as age and gender.

the non-inferiority margin actually suggest a better outcome for the experimental group, however, this difference is not statistically significant [4].

Discussion

This study shows that the postoperative start of LMWH in the prophylaxis of thrombotic events in patients undergoing operations with opening the spinal canal is effective, without affecting safety or provoking additional complications, such as bleeding and delayed wound healing.

There is only limited data in literature on the effectiveness of postoperative LMWH prophylaxis after spine surgery, however, evidence has been put forward showing the effectiveness and safety, first administered 6h after knee or hip replacement surgery [16,17]. In case of total arthroplasty they show a low rate of Venous Thromboembolism (VTE) and major bleeding. Furthermore, prophylaxis with LMWH started 6h after surgery minimises the risk of spinal haematoma associated with spinal/epidural anaesthesia [16].

Our results did not show a significant difference in incidence rate ratios for patients starting pre- or postoperative with anticoagulant therapy and took it over the whole period of postoperative follow up. Even including confounders such as age and gender showed no increased incidence of VTE in the study group. However, we found a slight better outcome in rates of postoperative complications in the experimental group, although there was no statistically significant difference.

The chosen length of prophylactic treatment given in our study, 21 days in minor and 28 days in major spinal procedures, is based on current recommendations for general orthopaedic operations [3] although the North American Spine Society does not support an ideal duration for thromboprophylaxis [13]. By choosing a minimum duration of prophylaxis of 21 days at minor spinal procedures, we tried to avoid the risk of the so-called rebound phenomenon at 14 days of anticoagulant therapy, even though if there is only little evidence in literature for the existence of such a problem [18]. There were no clinical signs of hypercoagulability in the study goup as well as in the control group over the entire period of follow up.

The study shows no statistical significant decrease of bleeding during and haematoma after operation in the studygroup, even though there was a subjective impression of reducton of epidural bleeding, which is consistend with reports of minimising the risk of spinal bleeding associated with spinal/epidural anaesthesia in the observational study of Abad et al. [16].

In our study, there were no cases of thrombozytopenia or death during the study period.

A positive side - effect of this new way of LMWH prophylaxis was the reduction of treatment expenses by the omission of the preoperative subcutaneous injection.

Our study has potential shortcomings. It is obvious that our cohort is too small to reach a statistical power, but a multicenter study with a cohort including more than 10000 patients was unrealistic to perform.

Therefor we chose a non-inferiority design to compare the two different treatments [15]. Since there is hardly any prior data on the comparative effectiveness, or safety, of pre- versus postoperatively administered thrombo - prophylaxis, it was extremely difficult to define a statistically valid and clinically relevant non-inferiority margin. We used a commonly known and FDA approved method to establish our margin, although the preservation method has been shown to yield more conservative results [6]. Both suffer from a somewhat low power statistically, i.e. more stringent cut-off values could be used, but we impress upon our readers to remember that clinical meaning should outweigh statistical methodology. This is especially true for the rate ratio of complications, which implies the potential for a reduction of complication incidence by almost 50%.

In conclusion low molecular weight heparin started postoperatively after spinal surgery with opening the spinal canal and given for at least 21 days shows no increasing of thromboembolic events. Although our study shows a limited statistical power, it emphasises in synopsis with existing studies concerning postoperative prophylaxis in major orthopaedic operations the same level of effectiveness as given preoperatively. Furthermore it shows the potential for reduction of complication incidence and epidural bleeding.

Acknowledgement

Conflict of Interest: No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

Funding: No funding was obtained for his study.

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