Local tolerability of two low-molecular-weight heparins, nadroparin and enoxaparin

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Subcutaneous administration of low-molecular-weight heparins is associated with localised injection site reactions such as acute pain, bruising, induration, and haematomas. Repeated exposure to such painful procedures may adversely affect treatment compliance. The aim of this clinical trial was to assess local administration site tolerability, specifically pain intensity, after a single subcutaneous injection of two common low-molecular-weight heparins, nadroparin and enoxaparin, as compared to placebo.

A five-week, double-blind, placebo-controlled, single-centre, cross-over, phase IV trial was conducted in 15 healthy volunteers. Following a screening period, participants received a single sequence of subcutaneous injections of nadroparin calcium, enoxaparin sodium and sodium chloride 0.9% w/v (placebo) at each of three visits, after which a final safety follow-up visit was conducted. The primary outcome measurement was subjective acute pain measured using visual analogue and numeric rating scales.

Subjective pain at the injection site was significantly greater following enoxaparin injection, as compared to both nadroparin and placebo. Both enoxaparin and nadroparin administration resulted in more severe erythema, haematoma and oedema, as compared to placebo. As expected, only a few adverse events were reported, all of which were mild and resolved spontaneously.

Nadroparin presents favourable injection site tolerability in terms of reduced pain intensity and duration. Tolerability associated with different treatments, especially in terms of pain, is an important consideration at prescription because of its effect on patient adherence to treatment and ultimately the effectiveness of treatment.

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Introduction

Patients with cancer, and those in the intensive care unit (ICU), have a higher risk of developing venous thromboembolism (VTE; deep vein thrombosis [DVT] and pulmonary embolism [PE]).[1] Those who develop these thromboembolic complications have a higher risk of morbidity and mortality.[2] Low-molecular-weight heparins (LMWHs), a relatively old class of drugs, remain the anticoagulants of choice in many indications relevant to haematology and oncology.[3]

LMWHs are known to be well-tolerated and effective alternatives to unfractionated heparin, producing a more predictable anticoagulant response, and a more reliable pharmacokinetic profile with better bioavailability, longer half-life and a dose-independent clearance. Therefore, routine monitoring of the anticoagulant activity of LMWH is not necessary.[4] LMWHs activate antithrombin III, which inhibits coagulation factor Xa, essential for the conversion of prothrombin to thrombin, and hence prevents fibrin clot formation.[5] Both nadroparin calcium and enoxaparin sodium have been shown to have similar efficacy for the prevention of mortality and VTE and similar odds of major or minor bleeding, as well as comparable efficacy for the prevention of PE and DVT in hospitalised medical patients.[6]

In contrast to these advantages, the subcutaneous administration of LMWHs is associated with localised injection site reactions including acute pain, bruising, induration, and haematomas.[7,8] According to a study by Hadley et al.[9] more than 90% of heparin injections lead to bruising at the injection site. Injection site pain, haematoma, pruritus or oedema following subcutaneous administration of LMWH can be distressing and unpleasant for patients and repeated exposure to such painful procedures can adversely affect patients' psychological well-being, causing anxiety and disruption of body image.[10,11] This can lead to problems with treatment compliance as patients may avoid injections or the possible sites for subsequent injections may become limited.[7,10-14]

The need for compliance to anticoagulation treatment to reduce the risk of morbidity and mortality associated with VTE, DVT and PE prompted the primary objective of this clinical trial, which was to assess local administration site tolerability,

specifically pain intensity, after a single subcutaneous injection of placebo, nadroparin or enoxaparin. Secondary objectives included measuring objective, quantifiable local injection site reactions, such as erythema and oedema, and assessing subjective experiences of local injection site reactions, including burning sensation and itching.

Methods

Ethics approval and consent to participate

The study (protocol CSA-150-ASP-002) was approved by the University of Pretoria Research Ethics Committee (359/2015) and was registered with the National Health Research Ethics Committee (NHREC; Application no. 4157, DOH-27-0416-5157) and U.S. NIH (ClinicalTrials.gov, NCT03841396). The South African Medicines Control Council approval was also granted (N2/19/8/2). The study was conducted in accordance with ICH GCP and SA GCP guidelines, as well as guidelines governing clinical study conduct and the ethical principles contained in the Declaration of Helsinki. All participants provided written informed consent to participate in the trial.

Study population

A total of 15 healthy volunteers participated in this double-blinded, placebo-controlled, single-centre, phase IV clinical trial. Healthy volunteers were recruited from local areas surrounding the Clinical Research Unit, at the University of Pretoria, between June and July 2016. Participants were deemed eligible for enrolment in the trial if they were male or female, medically healthy, aged 18–55 years, had a healthy weight (females ≥ 45 kg; males ≥ 57 kg, with a body mass index of 18.5–29.9 kg/m^2), and could understand and give informed consent. Participants were excluded from the study if they had a known hypersensitivity to enoxaparin, nadroparin or any of the excipients present in any of the medications; if they were taking any anticoagulants, NSAIDs, glycoprotein IIb/IIIa inhibitors, thrombolytic agents, platelet–inhibitors, acetylsalicylic acid, sulfinpyrazone, quinine containing remedies or drinks, treprostinil, apixaban, drotrecogin or herbal supplements that may affect coagulation or hyperkalaemia aggravators, seven days prior to screening; if they were lactating; if they had an injury or surgery to the ears, eyes, brain or spinal cord in the previous 18 months; if they had abused alcohol or drugs in the previous year; or had previously taken part in a clinical trial involving enoxaparin and/or nadroparin. Participants were advised that they were free to withdraw from the trial at any time, for any reason, without prejudice. Seventeen participants were screened for eligibility to the study.

Study design

Following a seven-day screening period (Visit 1), eligible participants were enrolled at Visit 2 (day 1) during which they received their first administration of investigational medicinal product (IMP). Participants returned to the site one week (Visit 3; day 8) and two weeks (Visit 4; day 15) later for the second and third administrations of IMP, respectively. This was followed by a safety follow-up visit one week after the administration of the last dose of the study drug (Visit 5, day 22).

All participants received all treatments to minimise between-subject variability. Each participant received a subcutaneous injection of 0.4 ml enoxaparin sodium (4000 IU) at Visit 2, 0.4 ml NaCl 0.9% w/v (placebo) at Visit 3 and 0.4 ml nadroparin calcium (3800 IU) at Visit 4, in prefilled syringes containing clear solutions of the drug.

All participants were blindfolded and injected subcutaneously in the supine position by the same unblinded study nurse. The observing investigator did not observe the injection and only after the unblinded study nurse completed injection, was the investigator allowed to make their (blinded) observations. The injections were slowly administered over a period of 30 seconds for safety reasons and to minimise potential bruising. The needle sizes were as follows: nadroparin calcium, 27G; enoxaparin sodium, 30G; and placebo, 30G. Sizes differed due to commercial packaging. Respective injections were administered to different sites on the abdominal wall.

Participants were allowed to recover for one week between injections. This interval was deemed to be a sufficiently long enough period for healthy participants to recover from bruising and pain and to prevent any synergistic pain and tenderness experienced from the previous drug administration to affect future administrations.[15]

Outcome measures

In line with the primary objective of the trial, the primary outcome was subjective pain intensity at the injection site following a single subcutaneous injection of nadroparin, enoxaparin or placebo. Subjective pain scores were measured using both a 100-mm visual analogue (VAS) and an 11-point numeric rating (NRS) scale. Both scales were completed at set time intervals over a 30-minute period after IMP administration, i.e. 1, 3, 5, 10, 15 and 30 minutes after the injection.

Secondary outcome measures included:

- VAS and NRS scores of a burning sensation at the injection site following administration;
- VAS and NRS scores of pruritus at the injection site following administration;
- safety in terms of local injection site reactions, i.e. the degree of erythema, oedema and haematoma; and
- safety in terms of adverse events, haematology, clinical chemistry and urinalysis.

Haematoma, erythema and oedema were measured 10 and 30 minutes and 1, 2 and 3 days after the injection, using transparent millimetric paper.

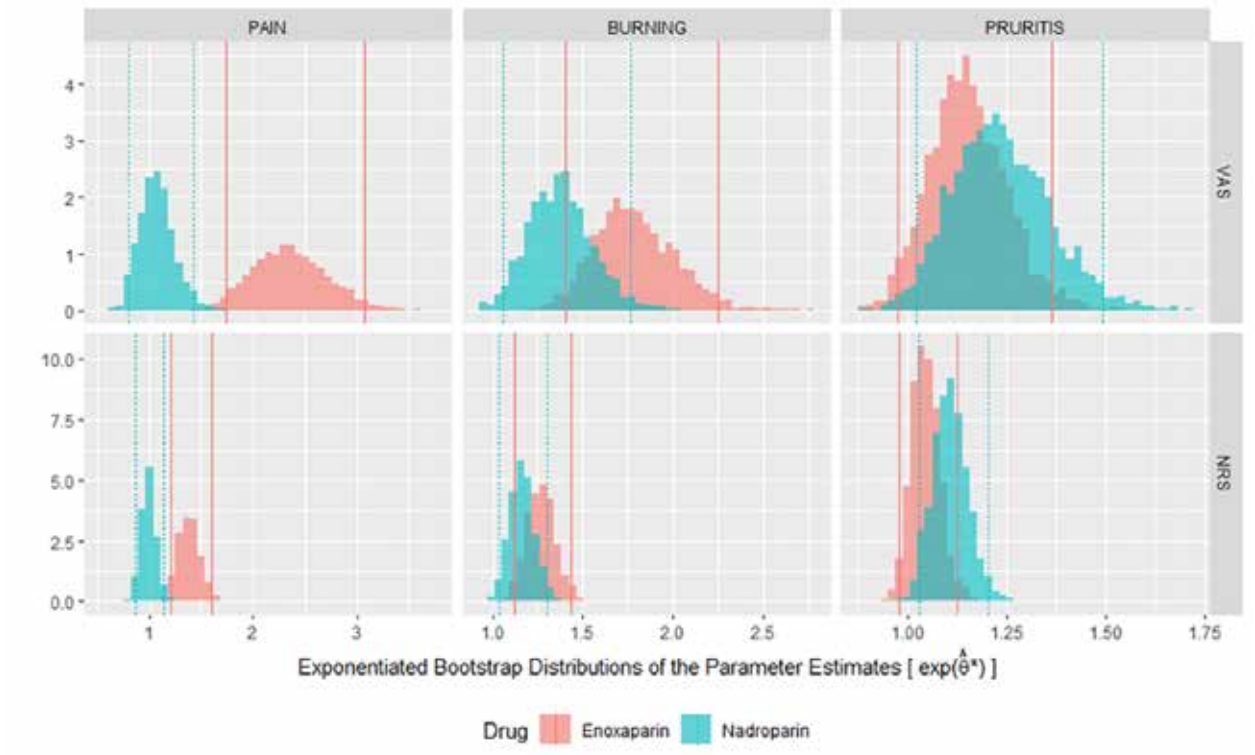

Figure 1: Influence of enoxaparin and nadroparin administration on acute pain burning and itching, relative to placebo, as measured using visual analogue (VAS, top row) and numeric rating (NRS, bottom row) scales. Distributions of the parameter estimates are depicted, with vertical lines representing the 95% confidence intervals associated with each distribution. Confidence intervals that do not overlap indicate significantly different influences on the measured outcomes ($P < 0.05$). Right shifted distributions are associated with greater VAS/NRS scores.

Statistical analysis

As this was an exploratory study in nature, no formal sample size estimation was performed. The sample size was selected based on previous research.[15] Due to the nature of the resulting data (diminishing pain intensity over time), data for the primary outcome was analysed as longitudinal data using exponential regression, with bootstrap sampling (for normality assumptions). VAS and NRS scores for pain were analysed in the same manner. All other data were analysed descriptively using nonparametric statistics. All enrolled participants were included in the analysis. Statistical analyses were performed using R version 3.6.0.[16]

Results

Demographics

A total of 17 volunteers were screened. Two volunteers were excluded for not meeting eligibility criteria. A total of 15 participants were enrolled (three males and 12 females, nine Black and six Caucasian), all of whom completed the trial and were included in the final analysis. The population had a mean age of 23.3 ± 2.9 years, a mean weight of 67.8 ± 15.2 kg, a mean height of 166.9 ± 10.2 cm and a mean body-mass index of 24.2 ± 3.9 kg/cm^2.

Primary and secondary outcomes

Regression results for pain, burning and pruritus provides distributions of the regression parameter estimates, which represent the influence of the active treatments, on the outcomes measured, relative to placebo (Figure 1). The greater the mean of the distribution of a particular drug, the greater the contribution of the drug to the perceived sensation, e.g. subjective pain. Vertical bars represent the upper and lower limits of the 95% confidence intervals associated with each distribution. Cases where the confidence intervals do not overlap present cases where the active treatments had significantly different influences on the outcomes measured ($P < 0.05$). Enoxaparin injections were associated with significantly greater VAS and NRS scores with respect to subjective pain. With respect to burning and pruritus, there were no significant differences observed between enoxaparin and nadroparin in either the VAS or NRS scales (Figure 1).

The majority of participants experienced pain for the first three minutes following injection. The median ± interquartile range (IQR) for the duration of pain was 3 ± 4 min, 4 ± 7.5 min and 4 ± 8.5 min for placebo, enoxaparin and nadroparin, respectively. The median ± IQR VAS scores for data collected during the first three minutes were 1 ± 6.5, 17 ± 25.75 and 1.5 ± 9.5 for placebo, enoxaparin and nadroparin, respectively. Median ± IQR NRS scores were 0 ± 1, 3 ± 3 and 1 ± 2, for the same order of treatments.

A similar trend was observed with a burning sensation following injection. Median ± IQR VAS scores were 1 ± 3.5, 6 ± 15 and 1 ± 7.75 for placebo, enoxaparin and nadroparin, respectively. Median ± IQR NRS scores were 0 ± 1, 1.5 ± 2 and

1 ± 1, in the same order. All three treatments produced similar degrees of pruritus with mainly overlapping distributions (Figure 1).

Solicited injection site reactions included erythema, haematoma and oedema (Table I). In general, both LMWHs elicited greater degrees of injection site reactions, as compared to placebo. Enoxaparin elicited the greatest degree of erythema and haematoma of the drugs administered, whereas both LMWHs induced the same degree of oedema. Interestingly, nadroparin appeared to produce delayed responses in terms of haematoma and oedema that only appeared 24 hours after injection in some participants.

Table I: Descriptive statistics (median and interquartile range) of the maximum injection site reactions observed over time following injection

Injection site reaction	Time point	Enoxaparin	Nadroparin	Placebo
Erythema (mm)	10 minutes	8 (15.5)	2.5 (17.25)	2.5 (6.25)
	30 minutes	3.5 (7)	4 (11.5)	3 (4.5)
	24 hours	3 (4.75)	3 (3.5)	0 (3)
	48 hours	1.5 (3.75)	1.5 (3.75)	0 (1.25)
	72 hours	0 (2.75)	0 (2.75)	0 (0)
Haematoma (mm)	10 minutes	2.5 (4)	0 (1.25)	0 (1.5)
	30 minutes	2.5 (3.25)	0 (2.25)	0 (0.75)
	24 hours	2.5 (3.75)	2 (4.5)	0 (0)
	48 hours	3 (3.5)	2 (4.75)	0 (0)
	72 hours	3 (3.75)	1.5 (4)	0 (0)
Oedema (mm)	10 minutes	3 (5.75)	0 (4.25)	0 (2.5)
	30 minutes	2.5 (4.75)	0 (4.75)	0 (2.5)
	24 hours	1 (3.5)	3 (4.25)	0 (0)
	48 hours	1 (2.5)	0 (3.25)	0 (0)
	72 hours	0 (2.5)	0 (1.5)	0 (0)

A total of six adverse events (AE) were experienced by a total of five participants during the study. Three of the six AEs were recorded before any investigational product had been administered and were therefore not treatment-emergent AEs. All AEs were mild in severity with a CTCAE grade of one. Four of the AEs were related to abnormal clinically significant laboratory measurements, of which two were due to increased aspartate aminotransferase, and two were due to increased eosinophil count. Two of the adverse events experienced were indicated to have a probable causal relationship to the treatment (eosinophilia). However, the treatment that was administered at the time was placebo. All AEs resolved completely. No unexpected adverse drug reactions were recorded, and no serious adverse events or deaths were reported.

Discussion

This phase IV clinical trial in healthy volunteers aimed to compare local injection site signs of intolerability of two LMWHs that are frequently used to prevent the high risk of morbidity and mortality in hospitalised patients. The primary outcome of this study indicated that the injection site pain intensity following a single dose subcutaneous administration of enoxaparin was significantly greater than that observed with nadroparin or placebo. This was observed with both kinds of subjective pain scales used, NRS and VAS. These findings of subjective acute pain reported here corroborate findings reported in a previous randomised, double-blind, three-period study comparing these two LMWHs in 12 healthy volunteers,[15] as well as an uncontrolled open clinical trial.[17] Pain intensity differed from individual to individual in the trial, which is expected due to the subjective nature of the outcome under scrutiny.

With respect to a burning sensation, regression showed that enoxaparin administration resulted in greater scores of a burning sensation (in both NRS and VAS scales), as compared to placebo and nadroparin. This was not a statistically significant result, but this may be due to the limited sample size, which also does not allow one to draw any conclusions regarding statistical equivalence from a statistical viewpoint. The same applies to the regression results obtained for pruritus.

In the present study, the injections were administered over a time of 30 seconds with the skin pinched, whereas earlier reports do not describe the administration technique used. The slow injection method was employed as a slower administration reduces injection site pain and less injury that can lead to subsequent bruising and hematomas.[8,10,18,19] Furthermore, keeping the skin pinched up while the medication is injected, and applying light pressure to the injection site to prevent the return of the drug after the injection, may also decrease the occurrence of bruising, haematoma and pain in subcutaneous heparin injections.[20]

Both LMWHs elicited greater responses in terms of these local injection site reactions. Enoxaparin caused greater erythema and haematoma than nadroparin and both LMWHs cause the same degree of oedema. An interesting trend was observed with respect to the time of peak response elicited by the two drugs. Enoxaparin appeared to induce an immediate local response, i.e. 10 min (erythema), 10 min – 72 hrs (haematoma), and 10 min (oedema). In contrast, it appears that nadroparin may cause a delayed local response with peak responses occurring at 30 min (erythema), 24–48 hrs (haematoma), and 24 hrs (oedema) after injection. Although this may be related to tissue penetration ability or tissue binding properties, the exact reason is not clear. Billon et al.[15] explained the decreased discomfort associated with nadroparin to the cationic salt composition of these preparations; nadroparin being a LMWH salified with calcium (3.8 mg in 0.4 ml), whereas enoxaparin is a LMWH salified with sodium (4.8 mg in 0.4 ml). They based this on an earlier study suggesting a better local tolerance of calcium versus sodium unfractionated heparin.[21]

In 2017 Van der Wall et al.[22] reported on an international cohort study, conducted at four sites, where they assessed

the adherence of 372 cancer patients treated with either enoxaparin or nadroparin for prolonged periods. They reported discontinuation rates due to side-effects of 30% and 10% for enoxaparin and nadroparin, respectively. Competing risk analysis showed a greater number of patients discontinuing treatment due to enoxaparin side-effects (with a hazard ratio of 3.4), where the most common reason for discontinuation was unacceptable pain at the injection site. The authors concluded that patients on enoxaparin were at a higher risk of discontinuation because of side-effects, compared to patients on nadroparin.

The current trial did not have a significant number of drop-outs due to pain, but participants were healthy volunteers and were only exposed to a single dose of each of the different treatments and the injections were spread a week apart to allow for recovery. In a population of ill patients who must administer these drugs more frequently and for longer periods of time, they may well experience a cumulative discomfort that could influence treatment adherence, like that reported by Van der Wall et al.[22]

Regarding safety, this study supported the fact that both LMWHs are safe and are well-tolerated. No subject withdrew from the study and only three treatment-emergent AEs were reported, all of which were mild in terms of severity and were completely resolved by trial close-out.

This current study has a few limitations. Firstly, the treatments were not given in a randomised sequence to the participants. However, both participants and observers were blinded to treatment which reduced the potential for any systemic bias. Secondly, this was a relatively small sample of healthy volunteers and a larger cohort would have been able to highlight additional differences that could not be detected in this trial.

Conclusion

In summary, nadroparin showed improved injection site tolerability in terms of subjective reactions, i.e. pain intensity and a burning sensation, as well as objective outcomes, i.e. erythema and haematoma. The increased discomfort associated with enoxaparin treatment may affect adherence among patients, specifically cancer patients on long-term treatment for VTE, as reported in literature. Interestingly, in this trial nadroparin injection was observed to cause some delayed injection site reactions, i.e. haematoma and oedema only observed 24 hours after injection. The reason for this is not clear. Both nadroparin and enoxaparin were safe and well-tolerated.

Conflict of interest

The authors declare that they have no financial or personal relationship(s) that may have inappropriately influenced them in writing this article.

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