Impact of injection speed and volume on perceived pain during subcutaneous injections into the abdomen and thigh: a single-centre, randomized controlled trial†

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Aim: The aim of this study was to assess pain associated with subcutaneous injection into the abdomen and thigh of different combinations of injection speeds and volumes.

Methods: The study was a single-centre, one-visit, double-blinded, randomized controlled trial in 82 adults with type 1 or type 2 diabetes receiving daily injections of insulin or glucagon-like peptide-1 (GLP-1) agonists. Participants received 17 subcutaneous injections (12 in abdomen, 5 in thigh) of saline at different injection speeds (150, 300 and 450 μl/s), with different volumes (400, 800, 1200 and 1600 μl), and two needle insertions without any injection. Pain was evaluated on a 100-mm visual analogue scale (VAS) (0 mm no pain, 100 mm worst pain) and on a yes/no scale for pain acceptability.

Results: Injection speed had no impact on injection pain (p = 0.833). Injection of larger volumes caused significantly more pain [VAS least square mean differences 1600 vs. 400 μl, 7.2 mm (95% confidence interval – CI; 4.6–9.7; p < 0.0001); 1600 vs. 800 μl, 7.2 mm (4.4–10.0; p = 0.0001); 1200 vs. 400 μl, 3.5 mm (0.4–6.6; p = 0.025) and 1200 vs. 800 μl, 3.6 mm (0.4–6.7; p = 0.027)]. Significantly more pain occurred in the thigh versus the abdomen (9.0 mm (6.7–11.3; p < 0.0001)).

Conclusions: Injection speed had no effect on injection pain, whereas higher injection volumes caused more pain. The results of this study may be of value for guiding patients to use the appropriate injection site and technique to reduce their injection pain. Furthermore, these findings may have important implications for the development of new injection devices and drug formulations for clinical practice.

Keywords: diabetes, injection speed, injection volume, subcutaneous injections

Introduction

Subcutaneous injections are used in numerous medical procedures including the administration of medicines, such as insulin, heparin and interferon-β, and monoclonal antibodies in chronic diseases [1–7]. Subcutaneous injection may result in discomfort and pain, which could lead to decreased adherence or even cessation of treatment. This might be particularly important for chronic conditions that require long-term use of injected therapies [8]. Therefore, it is important to completely understand the injection process to make injections as smooth and painless as possible.

In principle, patients are not concerned with individual factors that contribute to injection pain, such as the size of the needle, the formulation of the injected solution, the speed of injection or volume injected, but they consider the whole injection experience [9–11]. However, to understand the pain related to injections, individual factors need to be investigated and understood. Although there are studies that have investigated the effects of different aspects of subcutaneous injections on perception of pain, including the speed and duration of the injection [12], the effect of injection volume [13–16], injecting at different sites [17], the use of different formulations of a drug [7] and different injection devices [18], to our knowledge no systematic randomized controlled study to investigate these factors has been published. Furthermore, published data on the influence of injection speed and injection volume on injection-site pain are conflicting [12,15–17,19].

It remains unclear if simple measures, such as using a particular injection site or injection speed and/or volume, could minimize discomfort and pain of injections. The primary objective of this randomized, controlled trial, therefore, was to assess and describe pain in relation to subcutaneous injection into the abdomen and thigh of different combinations of injection speeds and injection volumes.

Methods

Study Design and Participants

The study was a single-centre, one-visit, double-blinded, randomized controlled trial in people with type 1 or type 2 diabetes receiving daily injections of insulin or GLP-1 agonists. Participants received 17 subcutaneous injections (12 in abdomen, 5 in thigh) of saline at different injection speeds (150, 300 and 450 μl/s), with different volumes (400, 800, 1200 and 1600 μl), and two needle insertions without any injection. Pain was evaluated on a 100-mm visual analogue scale (VAS) (0 mm no pain, 100 mm worst pain) and on a yes/no scale for pain acceptability.
2 diabetes, investigating pain during subcutaneous injections into the abdomen or thighs with different injection speeds and volumes. All study participants signed informed consent forms before entering the study and were free to withdraw from the study at any time. The study was conducted in accordance with the Declaration of Helsinki of 1964, as revised in 2008 [20], and Guidelines for Good Clinical Practice [21].

The trial population consisted of: White males or females aged 18–74 years with type 1 or type 2 diabetes; BMI ≥ 18.5 and ≤ 30.0 kg/m²; and self-injecting anticyclemic drugs [insulin or glucagon-like peptide-1 (GLP-1) agonist] for more than 6 months.

Exclusion criteria were: known or suspected hypersensitivity to trial products or related products; pregnancy measured by urine dip-stick at screening; receipt of any investigational medical product that could influence pain perception within 14 days before screening; injection of more than 40 units (or 400 μl) of insulin per injection or equivalent volume for GLP-1 agonists at study entry; continuous subcutaneous insulin infusion and/or continuous glucose monitoring use within the last 6 months; intake of any pain-relieving or analgesic drugs within the last week; intake of alcohol within the last 24 h (self-reported) or a positive result of an alcohol breath test; intake of illicit drugs within the last 48 h (self-reported) or a positive result of a urine drug screen; smokers or ex-smokers who used nicotine withdrawal products during the previous 6 months; known skin disease in the injection area or that could affect pain perception; moderate-to-severe lipodystrophy as evaluated by the investigator; severe neuropathy; anticoagulant treatment within the last month (low dose aspirin in cardiovascular prophylactic doses was allowed, but not on the day of the injections); any chronic disorder or severe disease which, in the opinion of the investigator, could jeopardize the safety of the person or their compliance with the protocol.

The study consisted of an informed consent and trial visit, during which all injections were administered over 5 h (all injections in the study were administered during the same time of day to exclude any influence of diurnal variation on pain perception) and trial participants stayed at the centre for at least 1 h after the last injection to assess injection-site reactions and adverse events (AEs). A telephone follow-up visit was conducted 24–48 h after the trial visit to further assess the development of injection-site reactions and AEs. If an injection-site reaction or AE had occurred the participant returned to the trial centre for further assessment.

Randomization
Novo Nordisk A/S provided each randomization number, which was identified by a unique sealed code that was opened by a trial nurse at the time a participant was randomized. Eligible participants were allocated a sequential randomization number. The injection speed and volume were administered according to the randomization schedule and treatment sequence, which was generated in blocks of 13. The investigator assessing injection-site reactions was blinded to the injection speed and volume sequence at all times.

Procedures
After randomization and before the first injection, participants were asked to complete a positive and negative affect schedule (PANAS) questionnaire, providing information relating to their mood, emotions and well-being. Each of the 20 questions in the PANAS questionnaire was rated on a 5-point scale (e.g. ranging from not at all interested to extremely interested) [22].

Participants received a total of 17 subcutaneous injections (12 in abdomen and 5 in thighs) of 0.9% sodium chloride solution at different injection speeds (150, 300 and 450 μl/s) and of different volumes (400, 800, 1200 and 1600 μl) as well as 2 needle insertions (without any injection, 1 in the abdomen and 1 in the thigh). The trial design was composed of a series of 13 × 13 Latin squares for the abdomen (all 12 speed/volume combinations and a needle insertion) and a series of 6 × 6 Latin squares for the thighs (5 selected speed/volume combinations and a needle insertion). All 19 injections were administered in the same prespecified order of injection sites for all participants in order to reduce variation in the study, but the speed and volume of injections (treatment sequence) were randomized.

The duration of injections ranged from 0.9 s for 400 μl at 450 μl/s to 10.7 s for 1600 μl at 150 μl/s. All needles were kept in the skin for 15–20 s in order to blind the injection speed and volume combination for the patients, and a new needle was used for each injection. The sodium chloride solution was at room temperature (20–25°C) at the time of injection. All injections and needle insertions were performed with a 30G × 6 mm thin-walled single-use luer-lock needle (TSK laboratories, Oirschot, the Netherlands) attached to a single-use 10 ml plastic syringe (ONCE Medical, Samut Sakhon, Thailand), and the injections were administered via a programmable syringe pump (Harvard Apparatus, Holliston, MA, USA).

Assessments
Participants recorded their perceived pain approximately 1 min after each injection, except for the first three injections, which were rated 1 min after the third injection to give participants the ability to evaluate the three pain perceptions relative to each other. Pain perception was evaluated on a 100 mm electronic visual analogue scale (VAS) (0 mm = no pain and 100 mm = worst pain). Acceptance of pain was rated as ‘yes’ or ‘no’ after each pain rating. The participants were asked to answer the question: ‘Would this pain be acceptable for your diabetes treatment?’.

Backflow from the injection site was measured 2 min after each injection by placing a filter paper over the injection site until all liquid was absorbed onto the paper. The size of the wet spot on the filter paper served as a measure of the backflow and was estimated using a backflow evaluation scale for comparison.

Local injection-site reactions (haematoma, haemorrhage, bruising, erythema and oedema formation) were assessed at three time points: acute, approximately 10 min after each injection; short term, at least 1 h after each injection; and long term, 20–48 h after each injection. Therefore, each unique local injection-site reaction could be registered and rated up to three times. All AEs observed by the investigator or reported spontaneously by the participants were recorded.
Statistical Analyses

The data for pain and backflow were analysed using linear mixed models, using injection speed, volume and injection site as fixed effects and participant as a random effect. Treatment effects were expressed as least square mean (LSM) differences with 95% confidence intervals (CI). The data for pain acceptance were analysed using generalized linear mixed models (logistic regression models), using injection speed, volume and region as fixed effects and participant as a random effect. Treatment effects were expressed as odds ratios between factor levels and corresponding 95% CI. No adjustments for multiple testing were carried out.

Results

In total, 82 participants were randomized. Two participants missed one injection each (received 16 subcutaneous injections and 2 needle insertions), one because of a pump failure and one because the participant moved after the needle was inserted and the intended volume was not administered. The baseline characteristics of participants are shown in Table 1. The psychological well-being mean positive PANAS score was 32.0 (range 17.0–47.0) and the mean negative PANAS score was 11.6 (range 10.0–22.0) indicating that participants were in the normal psychological well-being range [23].

Pain scores for most injections were at the lower end of the 0–100 VAS scale (Figure 1). For the pain assessments, there were no statistically significant interactions between region, speed and volume; thus, the models were adapted so that their effects could be evaluated separately.

Speed of injection had no impact on participants’ perception of injection pain (p = 0.833; Figures 1 and 2).

Injection of larger volumes (1200 and 1600 μl) was associated with higher perception of pain than lower volumes (Figures 1 and 2). Significantly more pain was recorded for 1200 μl versus 400 μl (p = 0.025) and 1200 μl versus 800 μl (p = 0.027; Figure 2). Significantly higher pain was associated with injection of 1600 μl than with lower volumes (Figure 2; 1600 μl vs. 400 μl and 800 μl, p < 0.0001, 1600 μl vs. 1200 μl p = 0.020). Injection volumes of 1200 and 1600 μl were associated with higher injection pain than needle insertions, whereas injection volumes of 400 and 800 μl caused injection pain scores that were similar to those of the needle insertions.

A higher proportion of subcutaneous injections administered to the abdomen (91.8%) were rated as acceptable compared with the thigh (79.4%; odds ratio 3.7, 95% CI 2.4–5.5, p < 0.0001). For each of the 19 injections, participant responses were divided into two groups according to acceptability of the injection pain (acceptable and unacceptable) and the mean was calculated. The range of these mean VAS scores for acceptable injections was 10–20 mm compared with the range of mean VAS scores for unacceptable injections of 45–75 mm. Needle insertions alone caused some individuals unacceptable pain [thigh 13 out of 82 (15.9%), abdomen 6 of 82 (7.3%)]. More pain was associated with injections into the thigh compared with the abdomen (LSM difference 9.0 mm, 95% CI 6.7–11.3; p < 0.0001, Figure 1).

Table 1. Study participants’ characteristics.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean ± s.d. (range)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>54.3 ± 11.9 (22–74)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>32 (39) : 50 (61)</td>
</tr>
<tr>
<td>White race, n (%)</td>
<td>82 (100)</td>
</tr>
<tr>
<td>Type of diabetes, n (%)</td>
<td>47 (57) : 35 (43)</td>
</tr>
<tr>
<td>Duration of diabetes, years</td>
<td>17.9 ± 11.3 (0.8–54.3)</td>
</tr>
<tr>
<td>Body weight, kg</td>
<td>79.3 ± 11.8 (56.0–106.0)</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>26.4 ± 2.6 (20.4–29.9)</td>
</tr>
<tr>
<td>HbA1c, %</td>
<td>7.7 ± 1.1 (5.2–10.5)</td>
</tr>
</tbody>
</table>

*Unless otherwise noted in first column.
this respect, our study shows that fast injection speed of 450 μl/s may represent a relevant range and it shows that within this range of injection speeds, patients may experience more pain or injection-site reactions compared with devices with slower injection speeds. The results of this study may be of value for guiding patients to use the appropriate injection device and technique to reduce their injection pain.

Our findings showed that pain increased with increasing injection volumes, which is in line with other similar studies [13,15]. Undoubtedly, injections of formulations of drugs with lower volumes may have some clinical benefits for patients prone to injection-site pain. However, there are a number of variables reported in other studies that should be taken into account because they may have influenced the perception of pain in these studies. For example, one study reported that higher injection volumes caused increased injection pain but the presence of glycerine – a vasoactive component – calls into question whether it was injection volume or a higher volume of a vasoactive compound that might have been responsible for the higher injection pain with larger volumes [16]. Indeed, there are a number of other factors that can influence the perception of injection pain. Changing the pH of a solution prior to injection [26], changing the buffer of injectable solutions [19], and/or using a smaller needle size can significantly alter injection-site pain [27].

Our study shows that approximately 9 of 10 needle insertions in the abdomen and 8 of 10 needle insertions in the thighs were associated with acceptable levels of pain. Nevertheless, injections administered in the thighs caused significantly more pain than injections administered in the abdomen, which is in line with findings from other studies [17,28].

Interestingly, some participants in our study reported pain (including unacceptable pain) for needle insertions alone, indicating needle insertions per se can cause pain. Indeed, the VAS scores for needle insertions were similar to the VAS scores obtained for the 400 and 800 μl volumes which may infer that no additional pain is perceived at low volumes even at fast injection speeds compared to the needle insertion itself. In another study, needle insertions without injection also resulted in some participants reporting unacceptable pain due to a vascular reaction that was triggered within the subcutaneous tissue as the needle was inserted [29].

Other findings from our study revealed that backflow was low (97% of recorded backflow events were <10 μl), and is thus not likely to have an impact on the pharmacological effect when injecting a drug.

The psychological well-being of the participants prior to receiving injections was in the normal range, and therefore was unlikely to have had an influence on the perception of injection pain [23]. Also, within the study, day-to-day physical and psychological background variability in pain perception was minimized by performing the injections within a short timeframe (5 h during the same period of the day in the afternoon) for all participants. Safety analysis recorded mostly mild injection-site reactions with no major safety issues.

One limitation of our study was that, in order to keep the number of injections to an acceptable level, not all injection speeds and volume combinations were injected into the

### Table 2. Number of local injection-site reactions by assessment time point.

<table>
<thead>
<tr>
<th>Assessment time point*</th>
<th>Haematoma</th>
<th>Haemorrhage</th>
<th>Erythema</th>
<th>Bruising</th>
<th>Oedema</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 ± 3 min</td>
<td>25</td>
<td>15</td>
<td>333</td>
<td>118</td>
<td>8</td>
<td>499</td>
</tr>
<tr>
<td>1–6 h</td>
<td>21</td>
<td>22</td>
<td>405</td>
<td>111</td>
<td>25</td>
<td>584</td>
</tr>
<tr>
<td>20–48 h</td>
<td>22</td>
<td>0</td>
<td>54</td>
<td>26</td>
<td>1</td>
<td>103</td>
</tr>
</tbody>
</table>

*The same injection-site reactions could potentially be rated and registered at more than one time point.

Discussion

Our study showed that the injection speeds (150, 300 and 450 μl/s) investigated in this study had no effect on the perception of injection pain. The study also showed that injection pain increased with injection volumes ≥1200 μl and injection pain was higher in the thighs than in the abdomen with all injection speeds and volumes.

Conflicting results have been published on the effect of injection speed on injection pain [12,24,25]. For example, one study reported that the severity of injection pain was higher in patients who received a 1000 μl subcutaneous injection of lidocaine into the forearms over 5 s (200 μl/s) compared with the same volume over a 30 s (33 μl/s) period [25]. Likewise, injection of 200 μl of heparin over a 10-s interval (20 μl/s) or a 30-s interval (7 μl/s) into the abdomen resulted in more intense injection-site pain at the faster injection speed [24]. Conversely, another study reported no difference in injection pain in patients who received 1000 μl of buffered or unbuffered lidocaine injected into the dorsum of the hands at either 100 or 1000 μl/s [12]. The difference between these findings and our study may be due to a number of factors including differences in the delivery method between the studies. Previous studies used manual injection to achieve the selected injection speeds, while our study used an injection device to reliably achieve the selected injection speeds. Other differences between our study and previous studies include variation in the injection site used between studies, and the different range of injection speeds used between studies. In conditions such as diabetes, little is known about the ‘normal’ range of injections speeds used by patients. Nonetheless, the range used in our study 150 to 450 μl/s may represent a relevant range and it shows that within this range of injection speeds, patients may experience more pain or injection-site reactions compared with devices with slower injection speeds.
thigh. This may have influenced the perception of pain scores between the thigh and abdomen. The results of this study tell us nothing about the relative pain of subcutaneous injection into other sites. Either whether injections into other sites would be more or less painful than injections in the thighs and abdomen, or whether the same speed/volume relationships with pain would be observed at other sites. In this study, we have investigated the impact of the general tissue reaction to injection speed and volume. However, local reactions to a specific drug or excipient properties, for example, pH, different concentrations or osmolarity of a drug would need to be investigated on an individual basis.

Our findings show that injection speed had no effect on injection pain, which has important implications for clinical practice because faster injection speeds associated with new injection devices should not impact on injection pain. However, higher injection volumes significantly increased injection pain and this may have direct implications when choosing which formulation/concentration of a drug to inject.

Acknowledgements

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Conflict of Interest

This study was funded by Novo Nordisk A/S, Bagsværd, Denmark. K. A. P., J. K., G. N. and T. S. are all employees of Novo Nordisk A/S. J. K., G. N. and T. S. all hold stock in Novo Nordisk A/S. T. H. has received research funds from Astellas, Becton Dickinson, Biocon, Boehringer Ingelheim, Dance Biopharm, Evolva, Hoffmann LaRoche, Johnson & Johnson, Eli Lilly, Lundbeck, Marvel, Novo Nordisk, Noxxon, Sanofi and Skye Pharma. In addition, T. H. has received speaker honoraria from Eli Lilly and Novo Nordisk, and travel grants from Novo Nordisk. T. H. is a member of advisory panels from Novo Nordisk and Skye Pharma. L. N., S. D. and E. Z. indicated that they had nothing to disclose.

All authors made a substantial contribution to the analysis and interpretation of the data and to the writing and revising of the manuscript. All authors reviewed the final version of the manuscript and gave permission to submit. Statistical analysis was provided by G. N.

References


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