Original Article

The effect of subcutaneous injection duration on patients receiving low-molecular-weight heparin: Evidence from a systematic review

Li-juan Yi a,1, Ting Shuaia,1, Xu Tian a,1, Zi Zenga, Li Ma a, Guo-min Song b,*

a Master degree candidate, Graduate College, Tianjin University of Traditional Chinese Medicine, Tianjin, 300193, China
b Director of Nursing, Nursing Department of Tianjin Hospital, Tianjin 400020, China

ARTICLE INFO

Article history:
Received 26 September 2015
Received in revised form
20 November 2015
Accepted 2 February 2016
Available online 16 April 2016

Keywords:
Heparin
Injections, subcutaneous
Injection duration
Systematic review
Meta-analysis

ABSTRACT

To assess the effect of the injection duration of subcutaneous low-molecular-weight heparin (LMWH) on pain and bruising in patients. Randomized controlled trials and quasi-experimental studies were searched for in four electronic databases. The pooled effect size was expressed as relative risk (RR) and mean difference (MD) with 95% confidence intervals (CI) for dichotomous and continuous data. Cochrane Q and p value were used to assess heterogeneity and the I² statistic was adopted to quantify the level. Finally, eight studies involving a total of 532 participants met our inclusion criteria. The slow (30 second) injection was associated with a reduction in pain intensity and duration, and lower bruising occurrence at 48–72 hours and 48 hours post injection. The bruising area was also smaller at 48 hours and 60 hours post injection. No differences were identified between the slow and fast (10 second) injection in bruising area and bruising occurrence at 24 hours and 60 hours post injection. With present evidences, slow injection of LMWH is beneficial to the patient’s well being, but further studies to identify the feasibility and standardization of the technique is recommended.

Copyright © 2016, Chinese Nursing Association. Production and hosting by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

1. Introduction

Pharmaceutical administration is an extremely important component of daily nursing service and extensively applied in emergency and rehabilitation settings. Some medicines, especially those administrated via subcutaneous (SC), intradermal or intramuscular, put extra responsibilities on nurses to explore safe and standard injection techniques to minimize unnecessary pain and potential complications [1,2].

Abbreviations: SC, subcutaneous; LWMH, low-molecular-weight-heparin; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analysis; JBI-MASTARI, Joanna Briggs Institute Meta-Analysis of Statistics Assessment and Review Instrument; RR, relative risk; MD, mean difference; RCTs, randomized controlled trials.

* Corresponding author.
E-mail address: songguomin134@163.com (G.-m. Song).
Peer review under responsibility of Chinese Nursing Association.
1 These authors have contributed equally to this article.
http://dx.doi.org/10.1016/j.ijnss.2016.02.008
2352-0132/2016, Chinese Nursing Association. Production and hosting by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).
As a type of heparin, low molecular weight heparin (LMWH) is only administered subcutaneously [3]. LMWH is frequently prescribed for preventing or treating venous thromboembolism because of its high bio-availability and predictable anticoagulant effect [4,5]. However, just like any other drugs, the use of LMWH does not come without possible adverse reactions. SC heparin preparations often cause adverse effects (AEs) such as bruising, pain, induration and hematoma at the injection site [6,7]. In this regard, previous studies have indicated that these local complications increased the patients physical and psychological discomfort and thus resulted in patients’ distrust in nurses’ efficiency [8,9]. In addition, the bruising can also restrict the possible area for future SC injection and reduce the opportunities for site rotation [10,11].

Literature related to the SC heparin injection have explored the potential factors which might minimize those side reactions and considered that the selection of syringe size and injection site, the application of ice and aspiration, and the injection duration can impact the occurrence of bruising and pain [12–15]. Among them, injection duration is an important influence factor. The researchers recommended giving SC LMWH injections over a 10-s duration [11,12], but which injection duration technique is ideal is far from clear.

Several Studies [16,17] previously have investigated the effects of injection duration on adverse outcomes at the injection site associated with SC administration of LMWH. Although exhaustive association trials have been undertaken to settle this issue, it hasn’t yet been obtained a definitive conclusion, and those results haven’t been recur. To provide more information for nursing practice, this systematic review examines existing knowledge to objectively assess the influence of two different injection techniques (10-s versus 30-s) on pain and bruising at the injection site in hospitalized patients who require LMWH therapy.

2. Material and methods

The Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) Statement [18] and Cochrane Handbook for Systematic Reviews of Interventions were adopted to guide the systematic review and meta-analysis [19]. All pooled analyses were grounded on previously published literature, and thus no ethical approval and patient informed consent were required.

2.1. Inclusion and exclusion criteria

We pre-specified the inclusion criteria for our study according to the PICOS format (which describes the participants, intervention, comparison, outcomes and study design). The details of this criterion were as following: (1) P: participants were considered meet the inclusion criteria if they were (a) 18 years or older; (b) administered LMWH therapy subcutaneously in hospital. (2) I and C: Two techniques of 30-s SC administration of LMWH in the one site of the abdomen as the intervention and 10-s SC administration of LMWH in the other site of the abdomen as the control were performed. (3) O: the pain intensity, the incidence of bruising and the size of bruising at the injection site were listed to be as primary outcome of measures and bruising dimensions and the site-pain duration were viewed as secondary outcomes. (4) S: Randomized controlled trials (RCTs) and quasi-experimental methodology would be appraised and included in the review.

It was ineligible for the study if the patients were currently on any other anticoagulant therapy. Study without a comparison group were excluded. Language of publication was imposed into English or Chinese through August, 2015.

2.2. Search strategies

We searched PubMed, EMBASE, the Cochrane Library, and the China National Knowledge Infrastructure (CNKI) to collect potential relevant randomized controlled trials (RCTs) and quasi-experimental studies through August, 2015. The search strategies utilized are shown in Appendix A. Next, the reference lists of included articles were manually searched to include any eligible studies.

2.3. Data abstraction

Two investigators (L-JY and TS) independently extracted the following basic information and essential continuous and binary data for expected outcome of interest from each included study using the predesigned data extraction form (Table 1): study ID which included first author and publication year, country, number of participants, demographics of subjects (age and gender), intervention, reported outcome of interest. The author would be contacted to acquire the complete data when necessary. If researchers provided inconsistent data for same outcome, we would obtain the most rational one. Any divergences between authors concerning the eligibility of a study were resolved by consulting a third author until a consensus was obtained (XT).

2.4. Quality appraisal

Risk of bias was assessed for RCTs using the Cochrane Risk of Bias Assessment tool (19) and for quasi-experimental study using the Joanna Briggs Institute Meta-Analysis of Statistics Assessment and Review Instrument (JBI-MASTARI) (see Appendix B) independently by two investigators (ZZ and LM). Disagreement was resolved by consulting a third investigator (G-MS). The Cochrane Risk of Bias Assessment tool addresses six specific domains as follows: sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and other issues. The risk of each included study was rated as ‘low bias risk’, ‘unclear bias risk’ or ‘high bias risk’ in accordance with the adequate degree of information extracted. The JBI-MASTARI tool based upon a quantity of critical questions fastened on the aspects of study design that research has shown to affect significantly the validity, for example, randomization, allocation, blinding and reporting. Each study was thus evaluated for quality utilizing the below checklist.
<table>
<thead>
<tr>
<th>Author (publication year)</th>
<th>Country</th>
<th>Target disease</th>
<th>Injection protocol</th>
<th>Age (E/C)</th>
<th>Sex (male/female)</th>
<th>Interventions</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zaybak A (2006)</td>
<td>Turkey</td>
<td>Cardiovascular disease, fractures, stroke</td>
<td>Insertion angle 90°; injection without drug aspiration; interval: 12h;</td>
<td>55.52 ± 12.37</td>
<td>25/25</td>
<td>Heparin was injected over 30 seconds on the left or right side of the abdomen</td>
<td>a + b + c + e + f</td>
</tr>
<tr>
<td>Sendir M (2015)</td>
<td>Turkey</td>
<td>Total hip arthroplasty, total knee arthroplasty</td>
<td>Insertion angle 90°; injection without drug aspiration; interval: 24h;</td>
<td>62.7 ± 8.83/57.9 ± 12.5</td>
<td>E: 7/13</td>
<td>Heparin was injected over 30 seconds on the one side of the abdomen</td>
<td>a + b + d</td>
</tr>
<tr>
<td>Dehghani K (2014)</td>
<td>Iran</td>
<td>Acute coronary syndrome</td>
<td>Insertion angle 90°; injection with drug aspiration; interval: 12h; drug dose: 60–80 mg Enoxaparin</td>
<td>35–75</td>
<td>36/34</td>
<td>Heparin was injected over 30 seconds on the left or right side of the abdomen</td>
<td>c + e</td>
</tr>
<tr>
<td>Dadaeen A (2015)</td>
<td>Iran</td>
<td>Cardiology, neurology, orthopedic</td>
<td>Insertion angle 90°; 27 gage needle; injection without drug aspiration; interval: 12h; drug dose: 40–80 mg Enoxaparin</td>
<td>47.78 ± 20.19</td>
<td>70/30</td>
<td>Heparin was injected over 30 seconds on the right side of the abdomen</td>
<td>a + c + e</td>
</tr>
<tr>
<td>Palese A (2013)</td>
<td>Italy</td>
<td>Unclear</td>
<td>Insertion angle 90°; 27.5 gage needle; syringe volume (0.4 mL); injection with drug aspiration; interval: 24h; drug dose: 4000 IU/0.4 mL Enoxaparin</td>
<td>74.8 ± 15.5</td>
<td>48/102</td>
<td>Heparin was injected over 30 seconds on the right side of the abdomen</td>
<td>b + d</td>
</tr>
<tr>
<td>Deng QX (2009)</td>
<td>China</td>
<td>Myocardial infarction, deep venous thrombosis, cerebral thrombosis angina</td>
<td>Insertion angle 90°; interval: 12 drug dose: 0.4 mL LMWH</td>
<td>57.6 ± 9.6</td>
<td>29/23</td>
<td>Heparin was injected over 30 seconds on the left side of the abdomen</td>
<td>a + b + c</td>
</tr>
<tr>
<td>Balci AR (2008)</td>
<td>Turkey</td>
<td>Chronic obstructive lung disease</td>
<td>Insertion angle 90°; 27 gage needle; injection without drug aspiration; interval: 24h; drug dose: 4500 IU/0.4 mL Tinzaparin, air lock: 0.2 mL inserted</td>
<td>60.02 ± 11.77</td>
<td>23/13</td>
<td>The second morning heparin was injected over 10 seconds on the left abdominal site</td>
<td>b + d + e</td>
</tr>
<tr>
<td>Chan H (2001)</td>
<td>Australia</td>
<td>Stroke</td>
<td>Insertion angle 90°; 27.5 gage needle; syringe volume (0.5 mL); injection without drug aspiration; interval: 12 h; drug dose: 5000 IU/0.2 mL Dalteparin; use air lock</td>
<td>40–85</td>
<td>20/14</td>
<td>Heparin was injected over 30 seconds on the left or right side of the abdomen</td>
<td>a + b + c + d + e</td>
</tr>
</tbody>
</table>

a = pain intensity; b = incidence of bruising; c = size of bruising; d = bruising dimensions; e = range of bruising size; f = pain duration.
2.5. Statistical analyses

The pain intensity and pain duration, the incidence, size and dimension of bruising at the injection site were calculated. Heterogeneity was evaluated using the Chi², corresponding P value. The level of heterogeneity was quantified by using I² statistic. If I² was >50%, the eligible study was considered to be heterogeneous and a random-effects model was conducted. In contrary, a fixed-effect model was performed. The pooled effect size was expressed as relative risk (RR) and mean difference (MD) with 95% confidence intervals (CI) for dichotomous and continuous data, respectively. A two-side P value of 0.05 indicates statistical significance. The descriptive analysis was adopted to objectively present the results across eligible study in terms of outcomes of interest which were ineligible for quantitative analysis. Considering different types of studies exist different risk of bias and measures of effect, We attempted to combine evidence respectively for RCTs and quasi-experimental studies. All pooled analyses were performed using Review Manager (RevMan) 5.3.0 (the Cochrane Collaboration, Copenhagen, Denmark).

3. Results

3.1. Search outcome

The search initially yielded 952 records. After screening title, abstract and full-text, a total of 8 studies were eligible for inclusion in the review. Among these trials, 5 were RCTs [2,4,8,20,21] and three were quasi-experimental non-randomized studies [7,9,22] (see Fig. 1). The full texts of these articles were obtained for analysis.

3.2. Characteristics of included trials

Seven articles [2,4,7–9,20,21] were published in English and one [22] in Chinese, and a total of 532 participants were included. The characteristics of 8 publications were abstracted and assessed (see Table 1).

3.3. Assessment of risk of bias

We presented an assessment of the methodological quality using Cochrane Collaboration’s tool for the five RCTs (see Table 2). Additionally, we critically applied the JBI-MAStARI tool for appraising the quality of incorporated quasi-experimental studies (see Table 3). Risk of bias for the five RCTs was discussed under the subheadings below.

3.3.1. Random sequence generation

Most randomized clinical trials lacked the description of the randomization process. All studies appeared to be randomized, but there was only one study [2] for which the method of sequence generation could be confirmed in sufficient detail to ascertain true randomization. So only one study was judged to be at low risk of bias and four studies at unclear risk of bias for this domain.

3.3.2. Allocation concealment

Only one study [21] was deemed to report allocation concealment adequately, so it is judged as being at low for risk of bias. For the rest of studies, method not stated, so they are judged at unclear risk of bias in this domain.

3.3.3. Blinding

Most of included studies [4,8,20,21] used a design with the subjects as their own control. It was hard to envisage how blinding of subjects could be applicable, because every participant had both slow and fast injections techniques, during the period of the study, participants would know which programs not be experienced. Because evaluation of the pain intensity mainly depended on the subjective judgment of participants, it could influence the outcomes in a large extent for whether implement blinding for participants. Meanwhile, it was also impossible to blind the personnel owing to the nature of intervention. Furthermore, only blinding of outcome assessment could be completed in these trials, two studies [4,21] not reported assessor blinding for pain evaluation, and one study [8] not reported assessor blinding for bruising measurement, according to the outcomes they reported, the domain of two articles were regarded as “unclear risk” and one as “low risk”. Other two studies [2,20] stated all injections and post-injection measurements were conducted by same researcher for both group, which produced high performance and detection bias. They were regarded as “high risk” in this domain.

3.3.4. Incomplete outcome data

There was no drop-outs or losses to follow up. Therefore, they were considered to be at low risk of attrition bias for this domain.

3.3.5. Selective report

All trials adequately reported all expected measure outcomes of interest in the paper and were deemed to be at low risk of bias.

3.3.6. Other potential source of bias

All studies were funded by non-commercial organizations. However, the description about other aspects of heparin injection was scarce, such as amount of heparin, syringe size, needle gage and injection volume. These factors may have an potential effect to the outcomes. To assess potential publication bias, we planned to perform a funnel plot and assess it asymmetry visually, however, only five studies included in this meta-analysis, it was not appropriate owing to lack of detecting power.

3.4. Intervention effects

3.4.1. Pain intensity

A total of 5 reports [2,4,7,8,22] including 3 RCTs and 2 quasi-experimental trials investigated the site-pain intensity. Pain assessment was performed immediately after each injection. Among them, Dadaeen et al. [4] applied Wilcoxon non-parametric test to compare pain severity between the two
interventions, so we only made a qualitative analysis. Two RCTs [2,8] and two quasi-experimental studies [7,22] were quantitatively synthesized with clinical and statistical homogeneity in the pain intensity, respectively. (RCTs: $P = 0.34$, $I^2 = 0$%; quasi-experimental studies: $P = 0.49$, $I^2 = 0$%), and thus a fixed-effect model of analysis were used. The treatment effects significantly differed between the two groups (RCTs: $MD = -8.73$, 95% CI: $-11.23$, $-6.24$, $P < 0.000$) (Fig. 2A, B). Moreover, Dadaeen et al. (4) used the Numeric Rating Scale to measure pain intensity, and the results showed the median and interquartile range of pain intensity scores in 10- and 30-s injection were 5 (4–7) and 3 (1.25–5), respectively, ($P < 0.001$).

### 3.4.2. Incidence of bruising

Six studies [2,7–9,21,22] which included 3 RCTs and 3 quasi-experimental studies employed the incidence of bruising as outcome. No overall heterogeneity for pooled existed in both types of studies (RCTs: $P = 0.48$, $I^2 = 0$%; quasi-experimental studies: $P = 0.65$, $I^2 = 0$%). On completion of the intervention period, the slow injection reduced the risk of occurring a bruising by 43% and 40%, severally. Subgroup analysis which was conducted on the basis of evaluating time demonstrated that the 30-s injection was more effective than 10-s injection in reducing the bruising occurrence (48–72 hours — RCTs: $RR = 0.63$, 95% CI: 0.46, 0.87, $P = 0.006$; 48 hours—RCTs: $RR = 0.53$, 95% CI: 0.36, 0.77, $P = 0.00$; 48 hours—quasi-experimental studies: $RR = 0.60$, 95% CI: 0.45, 0.81, $P = 0.00$; 48–72 hours—quasi-experimental studies: $RR = 0.63$, 95% CI: 0.42, 0.94, $P = 0.02$) except in 60 hours after injection (quasi-experimental studies: $RR = 0.56$, 95% CI: 0.30, 1.02, $P = 0.06$) (Fig. 3A, B).

### Table 2 – Risk of bias in randomized control trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Q1</th>
<th>Q2</th>
<th>Q3</th>
<th>Q4</th>
<th>Q5</th>
<th>Q6</th>
<th>Q7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dehghani K (2014)</td>
<td>U</td>
<td>U</td>
<td>H</td>
<td>H</td>
<td>L</td>
<td>L</td>
<td>U</td>
</tr>
<tr>
<td>Palese A (2013)</td>
<td>U</td>
<td>L</td>
<td>L</td>
<td>L</td>
<td>L</td>
<td>L</td>
<td>U</td>
</tr>
</tbody>
</table>

Q1 = random sequence; Q2 = allocation concealment; Q3 = blinding of participants and personnel; Q4 = blinding of outcome assessment; Q5 = incomplete outcome data; Q6 = selective reporting; Q7 = other bias; H = high bias; L = low bias; U = unclear bias.

### Table 3 – Risk of bias in quasi-experimental studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Q1</th>
<th>Q2</th>
<th>Q3</th>
<th>Q4</th>
<th>Q5</th>
<th>Q6</th>
<th>Q7</th>
<th>Q8</th>
<th>Q9</th>
<th>Q10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deng QX (2009)</td>
<td>NA</td>
<td>NA</td>
<td>U</td>
<td>Y</td>
<td>U</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Balci AR (2008)</td>
<td>NA</td>
<td>NA</td>
<td>U</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Chan H (2001)</td>
<td>NA</td>
<td>NA</td>
<td>U</td>
<td>Y</td>
<td>U</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
</tbody>
</table>

Y = Yes; N = No; U = Unclear; NA = Not Applicable; See Appendix B for question list.
A) Meta-analyses for pain intensity (RCTs). Meta-analysis fixed-effects estimates were used. B) Meta-analyses for pain intensity (quasi-experimental studies). Meta-analysis fixed-effects estimates were used.

---

Fig. 2 – A) Meta-analyses for incidence of bruising (RCTs). Meta-analysis fixed-effects estimates were used. B) Meta-analyses for incidence of bruising (quasi-experimental studies). Meta-analysis fixed-effects estimates were used.
3.4.3. **Bruising area**

A total of 6 articles [2, 4, 7, 8, 20, 22] which divided into 4 RCTs and 2 quasi-experimental studies reported the bruising area. The bruising area was marked on a transparent measuring paper or talc and calculated in mm². Among them, Sendir et al. [2] used a completely different method to measure the surface area of bruise tracings, this heterogeneity might reduce the comparability of the available results, and thus we only made a description for it.

Sub-group analysis was conducted due to the different follow-up. For three RCTs [4, 8, 20], pooled result revealed slow injection has smaller size of bruises compared with fast injection at 48h follow-up (48 hours: MD = -21.79, 95% CI: -23.77, -19.82, P < 0.000). However, no difference was identified between the two techniques at both 24 and 72 hours follow-up (24 hours: MD = 18.71, 95% CI: -18.67, 56.09, P = 0.33; 72 hours: MD = -88.40, 95% CI: -22.16, 44.36, P = 0.19) (Fig. 4). Sendir et al. [2] concluded that an SC injection duration of 30 seconds can result in significantly smaller bruises at 48, 60 and 72 hours after injection. For two quasi-experimental studies [7, 22], considering the different injection protocols (drugs, doses and intervals) adopted, we only made a narrative analysis. Chan et al. [7] demonstrated that there was significantly difference between two techniques at both 48 hours (Z = -4.542, P = 0.000) and 60 hours (Z = -4.569, P = 0.000) after each injection. The obtained results conducted by Deng et al. [22] showed the bruise was of bigger size in fast injection technique compared to slow injection technique at both 48 hours (P = 0.008) and 72 hours (P = 0.016) post injection. The conflicting conclusions is likely, whereas, to ascribable to the inappropriate timing of bruise data collection. According to the evidence available, the bruising usually peaks at 48 hours and tends to resolution around 72 hours after the use of LMWH [23, 24].

3.4.4. **Bruising dimension**

One RCT [21] and one quasi-experimental study [9] were involved in this indicator. As the difference of studies types exist, we only made a descriptive analysis. Balci et al. [9] considered the slow injection has larger bruises than the fast injection at 48 hours after injection (P = 0.000), but Palese et al. [21] found no difference in average bruising dimension between treatments at the same time (P = 0.661). This inconsistency caused by the various measurement methods was used to measure diameter extension. The former measured the maximum dimensions only when the shape is irregular, however, the latter recorded the maximum dimension of the bruise whether the shape is regular or not.

3.4.5. **Pain duration**

One RCT [8] and one quasi-experimental study [22] employed the pain duration as outcomes. To determine this outcome, the patients were asked to state the start and end values of their pain. As studies types differ, we only made a qualitative analysis. Both studies demonstrated pain period was shortened following the 30-s injections compared with 10-s injections (P = 0.000 and P = 0.030, respectively).

### 4. Discuss

#### 4.1. Necessity

The SC administration of the anticoagulant LMWH is a regularly performed nursing intervention. Since LWMH inhibit blood coagulation and needle punctures injury the skin tissue [1, 25], thus it tends to cause bruising and pain at the injection site. Epidemiology indicates the incidence levels of local bruising vary considerably, range from 20.6% to 88.9% after LMWH administration [7, 9]. With a view to easing the pain and improving patients’ satisfaction, it is incumbent upon health care professional to investigate the most appropriate SC administration technique of LMWH by manipulated controlling factors. From the physiological perspective, administrating an injection slowly can reduce pain and bruising caused by increased tissue pressure trauma [26]. However, the application of the injection duration not yet formed unified regulations so far.

#### 4.2. Summary of main results

Take into account a short of data from only RCTs; we widened our inclusion criteria from RCTs and quasi-experimental studies to make an attempt to increase the number of studies.

---

**Table 1:**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>slow injection</th>
<th>fast injection</th>
<th>Mean Difference</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(IV, Fixed, 95% CI)</td>
<td>(IV, Fixed, 95% CI)</td>
<td>(IV, Fixed, 95% CI)</td>
<td>(IV, Fixed, 95% CI)</td>
</tr>
<tr>
<td>3.1.1.34b</td>
<td>51.97</td>
<td>142.02</td>
<td>70</td>
<td>33.26</td>
</tr>
<tr>
<td>Katjia Dehghani 2014</td>
<td>51.97</td>
<td>142.02</td>
<td>70</td>
<td>33.26</td>
</tr>
<tr>
<td>Heterogeneity: Not applicable</td>
<td>Test for overall effect: Z = 0.08 (P = 0.33)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.1.2.34h</td>
<td>23.69</td>
<td>32.7</td>
<td>50</td>
<td>45.53</td>
</tr>
<tr>
<td>Dawson, A. 2015</td>
<td>58.23</td>
<td>143</td>
<td>70</td>
<td>47.96</td>
</tr>
<tr>
<td>Heterogeneity: Not applicable</td>
<td>Test for overall effect: Z = 2.71 (P = 0.006)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.1.4.72h</td>
<td>21.72</td>
<td>76.16</td>
<td>50</td>
<td>110.12</td>
</tr>
<tr>
<td>Zaybek A 2006</td>
<td>21.72</td>
<td>76.16</td>
<td>50</td>
<td>110.12</td>
</tr>
<tr>
<td>Heterogeneity: Not applicable</td>
<td>Test for overall effect: Z = 1.31 (P = 0.19)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Test for subgroup differences: Ch² = 5.47, df = 2 (P = 0.06), P = 63.4%
available information. Eventually, Five RCTs and three quasi-experimental studies met our inclusion criteria. This meta-analysis found evidence that the slow injection technique could effectively improve pain intensity and pain period measured over time and decrease bruising occurrence at both 48–72 and 48 hours follow-up and the bruising size at both 48 and 60 hours follow-up compare to the fast injection technique. But no difference was identified in bruising area and bruising occurrence between groups measured at 24 hours and 60 hours follow-up. Furthermore, due to insufficient data, we cannot draw a reliable conclusion of whether the slow injection technique can reduce the bruising area at 72 hours follow-up and bruising dimension at 48 hours follow-up.

4.3. Mechanism

Possible explanations that why slow injection technique may be effective in pain and bruising are explored: a) SC administration delivers the LMWH into the interstitial space of the hypodermis which contains few arterioles and venues, and thus unabsorbed drugs concentrated the injection site [27]. Slow injection can accelerating drug absorption, reducing tissue stimulation and damage at the injection site [28,29]; b) A fast injection technique cause tissue damage due to the rising strength giving to the tissue, while slow injection allow more time for the SC tissue to accommodate the drug, lowering the tissue pressure in the puncture site, and thus result in less nerve fiber endings and tissue injury from mechanical trauma [15,30].

4.4. Limitation

We performed this systematic review to generate more accurate results based on enlarged the cumulative sample size, several limitations were need to be acknowledged. Firstly, incomplete search and the restriction of the language can reduce power of pooled results. Secondly, the subjects of included studies suffered different diseases would limit the generalization of evidence. It should be considered adjust the injection period appropriately to accommodate different groups. Third, scarce articles provided a detailed description about whether patients were taking the analgesic medications in process of research, it is an undeniable fact that the usage of analgesic medications affected the assessment of the pain. Except that, injection technique for participants should be more standardized and systematic. We discovered from injection protocol that it still not formed a consensus in the selection of gage needle, the application of aspiration and air lock. These factors may impair the heterogeneity among these studies. So we hope researchers do more studies to provide more standardized, scientific and rationalized way for clinical use.

4.5. Implications for practice and research

The current research provides a contribution to the precaution of local complications associated with SC administration of LMWH. Though ice application has already been proved effective in reducing site-pain [6,10], however, it requires additional nursing time and effort. Besides, the use of a larger syringe or a higher gage needle can also result in less tissue pressure trauma [12,31], but it is costly and waste limited resources. Comparing these methods above, slow injection technique may be more practical for nurses.

But there are some issues to think and tackle. Firstly, it is worth considering the feasibility of the technique. Administering a solution of less than 1 ml in 30 seconds is difficult, especially when assisting confused patients. Other research models that investigate the effect of intermediate injection duration (that is 15 and 20 seconds) for developing new interventions preventing local reactions related to LMWH are strongly recommended. Secondly, the extension of operation time need nurses focus more on keeping warm and protecting privacy of patients. Meanwhile, the studies which use to evaluate the different SC injection sites for LMWH therapy are needed. At present, it is only recommended that injections sites should have a sufficient amount of fat [32], however, whether the abdomen is the only or preferred site for SC injection is still unclear [13,33,34]. Except that, further studies need to pay attention to other outcomes, such as leakage of drugs and hematoma at the injection site. No included studies reported these indicators, but these outcomes have great value for assessing the effect of slow injection and worth to investigate in future studies.

5. Conclusions

Although some limitations may impair the power of this study, we concluded that slow injection can alleviate site-pain, reduce pain time, bruising occurrence and decrease the bruising size as a whole except some slight fluctuations following the measuring time. Thus the clinical practice of utilizing the slow injection as a proper method for SC LMWH injections was supported. In consideration of chance error, more large-scale and design-well prospective studies are warranted to further this conclusion.

Authors’ Contributions

L.-J. Yi, X. Tian and Shuai conceived the study. L.-J. Yi, X. Tian and T. Shuai collected the data and performed statistical analyses. Z. Zeng helped to collect the data. L.-J. Yi, X. Tian and L. Ma participated in the design, collected the data, and drafted the manuscript. All authors read and approved the final manuscript.

Conflicts of interest

The authors declare no funding and conflicts of interest. In addition, all authors reviewed the whole manuscript and approved current version to be considered for publication in Research in International Journal of Nursing Sciences®.

Acknowledgments

All authors would like to appreciate the editor and all staffs work in editorial office of Research in International Journal of Nursing Sciences®. Moreover, we also would like to appreciate Mr Harsh (Master degree candidate, international college, Nankai University) spent golden time to revise this manuscript.
## Appendix A

**Search strategy via PubMed**

<table>
<thead>
<tr>
<th>Search</th>
<th>Query</th>
<th>Items found</th>
</tr>
</thead>
<tbody>
<tr>
<td>#11</td>
<td>Search #4 AND #7 AND #10</td>
<td>409</td>
</tr>
<tr>
<td>#10</td>
<td>Search #8 OR #9</td>
<td>936477</td>
</tr>
<tr>
<td>#9</td>
<td>Search random*[Title/Abstract]</td>
<td>787844</td>
</tr>
<tr>
<td>#8</td>
<td>Search (“Randomized Controlled Trials as Topic”[Mesh]) OR “Randomized Controlled Trial”[Publication Type]</td>
<td>484103</td>
</tr>
<tr>
<td>#7</td>
<td>Search #5 OR #6</td>
<td>13759</td>
</tr>
<tr>
<td>#6</td>
<td>Search [(low-molecular-weight heparin][Title/Abstract]) OR low molecular weight heparin][Title/Abstract] OR LMWH][Title/Abstract]</td>
<td>8902</td>
</tr>
<tr>
<td>#5</td>
<td>Search “Heparin, Low-Molecular-Weight”[Mesh]</td>
<td>10264</td>
</tr>
<tr>
<td>#4</td>
<td>Search #1 OR #2 OR #3</td>
<td>49379</td>
</tr>
<tr>
<td>#3</td>
<td>Search injection duration*[Title/Abstract]</td>
<td>132</td>
</tr>
<tr>
<td>#2</td>
<td>Search (subcutaneous injection*[Title/Abstract]) OR SC injection*[Title/Abstract]</td>
<td>17726</td>
</tr>
<tr>
<td>#1</td>
<td>Search “Injections, Subcutaneous”[Mesh]</td>
<td>35400</td>
</tr>
</tbody>
</table>

## Appendix B

**JBI MASTARI Appraisal Tool for Experimental Studies**

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
<th>Unclear</th>
<th>Not Applicable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was the assignment to treatment groups truly random?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Were participants blinded to treatment allocation?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Was allocation to treatment groups concealed from the allocator?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Were the outcomes of people who withdrew described and included in the analysis?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Were those assessing the outcomes blind to the treatment allocation?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Were control and treatment groups comparable at entry?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Were groups treated identically other than for the named interventions?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Were outcomes measured in the same way for all groups?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Were outcomes measured in a reliable way?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Was appropriate statistical analysis used?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Overall appraisal:  Include □ Exclude □ Seek further info □

Comments (including reasons for exclusion): ______________________________
REFERENCES