REVIEWS

Subcutaneous administration technique of low-molecular-weight heparins: An integrative review

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Abstract

Anti-coagulant drugs for subcutaneous injection, like low-molecular-weight heparins (LMWH), are increasingly used to prevent and treat thromboembolic events, with local adverse reactions. The aim in this integrative review was to identify and analyze knowledge production about the most appropriate SC injection technique of LMWH to reduce hematomas, bruising and local pain. The following inclusion criteria were used: papers published in English, Spanish and Portuguese; between the first week of August 2001 and the last week of August 2012. Papers in which LMWH was compared with unfractionated heparin in the assessment of the outcomes and papers without statistical data analysis were excluded. The searches were undertaken in the electronic databases PubMed/MedLine, CINAHL, Scopus, Web of Science and LILACS/IBECS. The quality of the articles was assessed with the critical appraisal tool JBI MAStARI. The incidence of bruising ranged between 20%, when the application time of the injection was 30s, and 88.9% when it took 10s. In 50% of the studies, the authors concluded that LMWH injections taking 30s caused lower levels of bruising, with statistically significant differences, as well as a reduction in pain intensity in the injection site by up to 50%. The group that received LMWH through a prefilled syringe, with or without aspiration, showed lower levels of bruising. The formation of a skinfold, the 90º angle and the abdomen as the application site have been well documented in the literature. These findings are important for clinical nursing practice, as they found the elaboration of evidence-based care protocols and contribute to the improvement of patient care quality.

Key words

Subcutaneous injections, Low-molecular-weight heparins, Hematoma, Bruise, Pain

1 Introduction

Anti-coagulant drugs for subcutaneous (SC) injection, like low-molecular-weight heparins (LMWH) – enoxaparin, dalteparin, tinzaparin and fondaparinux, are increasingly used to prevent and treat thromboembolic events [1].

These drugs inhibit blood coagulation, in vivo and in vitro, through the binding of the antithrombin III with the Xa factor, causing a drop in thrombin and finally preventing the formation of the thrombin clot. The pharmacokinetic and pharmacodynamic particularities, such as high bioavailability, long half-life, more predictable anticoagulant response,

easy laboratory monitoring and less bleeding risk in comparison with unfractionated heparin contribute to the widespread use of LMWH in the hospital and home-care contexts [2-4].

Like other drugs, however, the use of LMWH does not come without possible adverse reactions (ADRs), even if used in therapeutic doses and administered correctly. The most frequent ADRs include hematomas, bruising and pain in the injection site, probably due to the local trauma that occurs during the SC injection [5, 6].

Epidemiology indicates incidence levels of local hematomas after LMWH administration between 40% and 88% [7, 8] and between 26.6% [6] and 88.9% [9] for bruising. Research affirms that the administration technique the nursing professional uses can influence the occurrence of these events and the pain intensity levels [5, 10, 11]. Factors like the injection site, size of needle, amount of heparin, applying, aspiration before the injection, post-injection massage and duration of injection can influence the occurrence of bruising [6]. Although inconclusive, earlier studies indicate that the manipulation of these variables is able to contribute to bruising and local pain intensity [5, 6, 8, 12-15]. Available research in the field of bruise occurrence and extension, published between 1984 and 2000 [6], showed that manipulation of one or more variables of administration may result in less intense local pain and bruising.

Medication administration by nurses demands knowledge and clinical reasoning, with a view to the expected outcome in the patient. As many services do not consider evidence regarding the LMWH administration technique and aiming to mitigate the occurrence of ADRs, the scope of this review was to identify and analyze knowledge production about the most appropriate SC administration technique of LMWH with a view to reducing hematomas, bruising and local pain.

Purpose of the review

The main purpose of this integrative review was to identify and analyze knowledge production about the most appropriate SC administration technique of LMWH with a view to reducing hematomas, bruising and local pain. The research question of the review is:

What evidence is available in the literature about SC administration techniques of LMWH to reduce hematomas, bruising and local pain?

2 Method and data

2.1 Design

This study used an integrative review as the research design. This integrative review has been conducted using Whittemore and Knaffl's [16] steps, which are: formulation of the problem, collection, evaluation, analysis and interpretation of the data and presentation of the results. The intent of an integrative review is to summarize pertinent research findings and to use clinical judgment to draw conclusions from the body of literature on a particular topic, so as to support and guide evidence-based nursing practice [17].

2.2 Literature Search

The literature search (see Figure 1) was conducted systematically [16, 18], through an electronic search of bibliographic databases using PubMed, MedLine, CINAHL, Scopus, Web of Science and LILACS/IBECS (Literatura Latino-Americana e do Caribe/Indice Bibliográfico Español em Ciencias de Salud). The studies were selected independently by two authors. In case of disagreement, a third author revised the selection according to the inclusion and exclusion criteria.

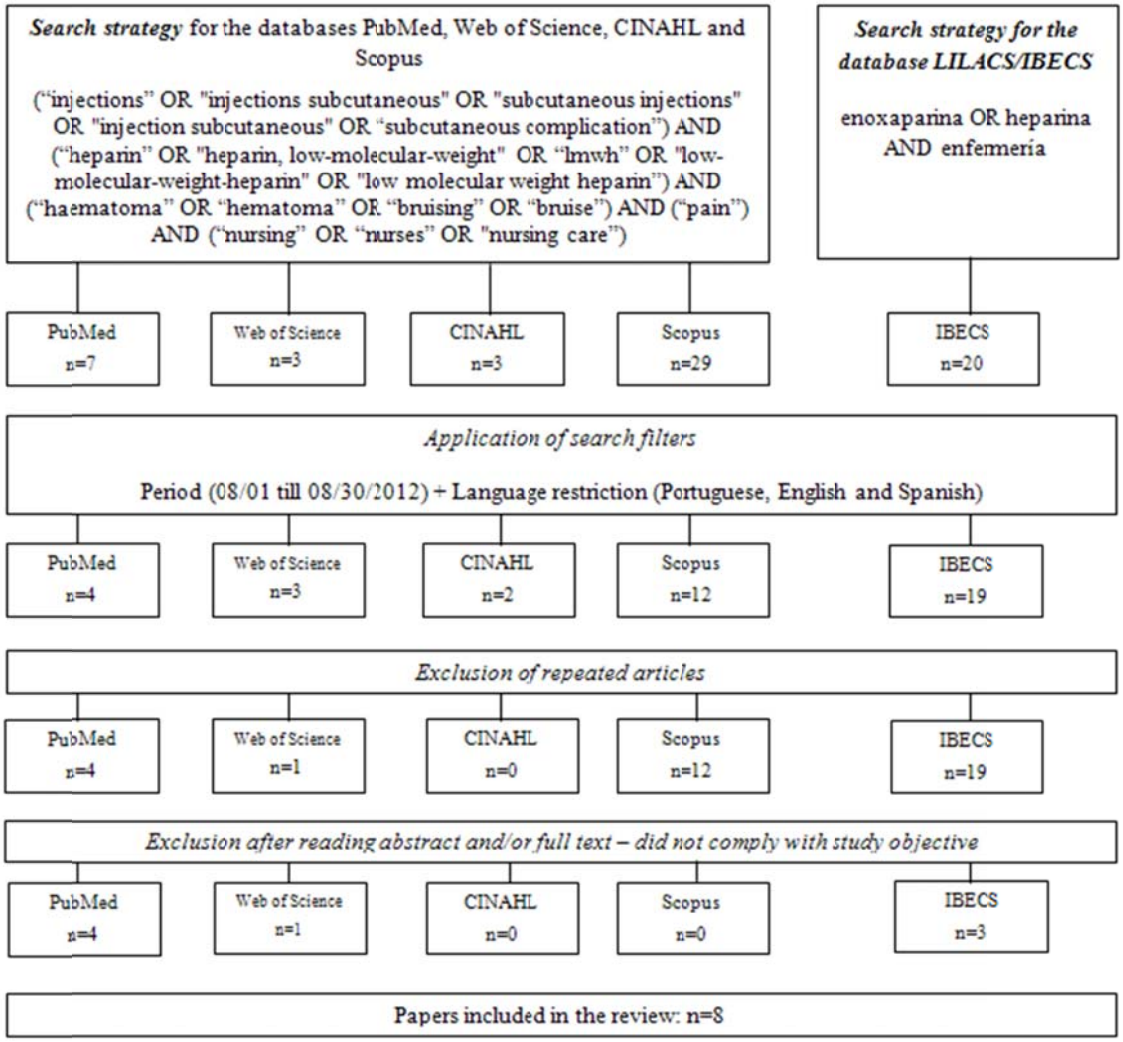

Figure 1. Study inclusion Flow Chart

2.3 Inclusion criteria

Studies published in English, Spanish and Portuguese, between the first week of August 2001 and the last week of August 2012, whose full version was available in the consulted electronic databases, about the SC administration technique of LMWH and the occurrence of hematomas, bruising and pain in the injection site in adult individuals, independently of the place of study.

2.4 Exclusion criteria

Duplicated studies, studies in which LMWH and unfractionated heparin were compared in the assessment of the outcomes, studies without statistical analysis of the data, literature reviews and dissertations were excluded.

2.5 Data analysis and evaluation

Data from the eight studies were extracted, including: author and year, sample, study design, intervention description, measures/outcomes, results, methodological strengths and limitations and conclusion, and were evaluated with the help of the JBI MAstARI tool. The selected studies according to MAStAri were scored between 5 and 8. The evaluation of research articles is presented in table 1 [19].

Table 1. Evaluation of selected studies (MAStARI evaluation points ranged from 5 to 8)

Studies n=8	Chan et al. (2001) Australia 5/10	Manrique et al. (2002) Spain 7/10	Robb et al. (2002) Canada 8/10	Gomez et al (2005) Spain 7/10
	Zaybak et al. (2007) Turkey 5/10	Akpinar et al. (2008) Turkey 6/10	Cortes et al. (2009) Spain 5/10	Palese et al. (2012) Italy 8/10

3 Results

3.1 Study characteristics and participants characteristics

The eight studies that met the inclusion criteria included 840 participants. Most studies were published in nursing journals (87.5%), undertaken in European countries (75%), with experimental and quasi-experimental designs (87.5%) and aimed at assessing technical aspects like the needle caliber [12], syringe type [20], injection administration time [6, 9, 21, 22] on the occurrence of outcomes. The study sample mostly consisted of men (76%), with a mean age ranging between 55.5 and 74.8 years. Half of the studies [12, 20-22] involved patients hospitalized at specialized cardiology units.

3.2 Outcomes, follow-up, strengths and weaknesses

Chan et al. [6] used a quasi-experimental design, involving 34 stroke patients with ages ranging from 41 to 85 years, with a mean age of 63.1 years (SD ± 9.82) for male and 65.7 (SD ± 13.17) for female patients. The average length of subcutaneous heparin therapy for this sample was 7.9 days (SD ±3.58). In this study, the influence of administration time (10s or 30s) on bruising and pain intensity was investigated. Results indicated that the injection of 10s sites had larger bruises than injection 30s sites, with a mean bruise size difference ranging from 23.16 to 24.67 mm^2, at both 48 hours (Z=± -4.542, *P*=0.000) and 60 hours (Z = ± -4.569, *P*=0.000) after injection. The log odds ratio coefficient indicated that females were 7.5 to 10 times more likely to bruise than males. The frequency of bruises was higher in female participants (78.6% to 85.7%), at both 48 and 60 hours after a 10s-injection than that of males (25%). There was no relationship between skinfold thickness and bruising at both 48hs (*P*=0.5925) and 60 hours (*P*=0.3230). The strength in this study was its homogeneous sample, as all participants were Caucasian and affected by ischemic strokes. The limitations were its small sample, nonrandomized sample, unequal number of male and female subjects and the non-randomized sequence of administering the injection.

Manrique et al. [23] developed a randomized controlled trial, involving 38 obese (n=19) and non- obese (n=19) patients, with or without the formation of a subcutaneous fold. The mean age was 69 years and 56% were males and 44% females. In obese subjects, there was a positive correlation between the non-folding technique and the absence of hematoma (*p*=0.001) and, in non-obese subjects, skin-folding acted as a protective factor against hematoma (*p*=0.001). The study was limited to a small sample of patients, with the randomized sample and the subcutaneous injection protocols for all patients as strong points.

Robb et al. [12] used a randomized trial design with 60 unstable angina or non-Q-wave myocardial infarction patients. The age ranged from 49 to 85 years for the tuberculin syringe (26 gauge, 3/8-in) group and from 39 to 88 years for the insulin syringe (30 gauge, 5/16-in). After each dose, patients were asked to rate the pain associated with the injection on a 10-unit numeric scale. There was no significant different between the tuberculin and insulin syringe group with regard to the mean largest hematoma size/patient (*p*=0.68). For pain on injection, there was no significant difference in mean pain scores between the two groups (*p*=0.10). The limitations in this study were the small sample and the assessment for the presence of hematomas every 12 hours, given that the reported time to peak bruising after subcutaneous injection is about 48 hours,

besides the different observers who obtained measurements, thereby subjecting the data to inter-observer variability. The strengths were the randomized trial study and the fact that nurses administered the LMWH based on current practice and recommendations from a pamphlet supplied by the manufacturer.

Gomez et al [20] performed a randomized clinical trial in 300 patients, distributed in four groups, according to whether the syringe was aspirated or not before injection and whether the syringe was prefilled or filled at the moment of administration. Of the study participants, 78% were women and the mean age was 63.2 years and 36.4% had obesity. The follow-up period was 10 days or for the duration of treatment when treatment was administered for less than 10 days. The bruising occurred in 60.6% of the participants, but the development of bruising was significantly lower in the prefilled group (p=0.048). The incidence of hematomas was larger in women (p<0.01), obese patients (p<0.01), and patients aged more than 60 years (p<0.05). The strengths were the large sample and the randomized clinical trial design. The limitations were the many variables (four techniques) and the lack of standard equipment/tools, procedure and subcutaneous injection technique for administering the LMWH, and the fact that the administration was not done by an expert nurse.

Zaybak et al. [21]: this study was a quasi-experimental research and the participants were hospitalized at the neurology, orthopedics and cardiology units of a university hospital. A total of 50 patients (50% women and 50% men) were included in the study. Twenty percent of the patients were between 20 and 45 years of age, 44% were between 46 and 60 and 36% were over 60 years old. The percentage of bruising was 64% for the 10-second injection and 42% for the 30-second injection (p<0.05). In addition, in case of slow heparin injection (30 seconds), the size of the bruising was smaller than for 10-second injections (p<0.05). Pain intensity and pain period were significantly lower for the 30-second injection than for the 10-second injection (p<0.001). The strengths were the standard equipment/tools, procedure and subcutaneous injection technique for the administration of the LMWH and the limitations were small number of subjects and the lack of a randomized design.

Akpinar et al. [9]: this quasi-experimental study included a total of 36 subjects with chronic obstructive bronchopathy in a surgical unit. The mean age range was 63.02 ±11.77. Thirteen subjects (36.1%) were women and 23 men. There were three injection techniques to administer the LMWH, the first injection took 10 seconds (technique A), the second 30 seconds (technique B), and the third 10 seconds, with withdrawal of the needle after a further 10 seconds (technique C). There was a significant difference between injection technique A and injection technique B (p=0.002), injection technique A and technique C (p=0.035) at 48 h after injection. About the occurrence of bruising between B and C, there was no difference (p=1.000). This study recommended 10- second injections with 10 seconds of waiting time, which may be more preferable in clinical practice because less time is needed to administer the heparin. The strengths were the administration of the injections by the same investigator and the standard equipment/tools, procedure and subcutaneous injection administration technique, while the limitations were the small sample and the non-randomized selection of region and treatment order.

Cortes et al. [24] used a prospective cohort design with 172 subjects from a clinical and a coronary intensive care unit. The mean age was 69 years and 61.6% were men. This study quantifies the incidence of secondary local complications after heparin administration and determines the risk factors. The average length of subcutaneous heparin therapy for this sample was nine days. The percentage of bruising was 46.8% and mean bruising size was 53 cm^2. The main risk factor correlations were: patients over 70 years of age (p=0.019); patients with heart diseases (p=0.002); overweight patients (p=0.029); abdominal perimeter larger than 106.66 cm (p=0.012; treatment time longer than 10.86 days (p=0.001); concomitant use with platelet anti-aggregates (p=0.009); accomplishment of cardiac catheterization (p=0.034). Local pain was reported in 10% of the sample. The strengths were larger sample, but there were no randomized patients or register about standard equipment/tools, procedure and subcutaneous injection technique for administering the LMWH.

Palese et al. [22]: the study had a quasi-experimental case crossover design, included a total 150 patients who received their first (10 seconds/treatment A) and second (30 seconds/treatment B) subcutaneous heparin injections at orthopedic units. The mean age was 74.8 ±15.5 and, about the gender, 68% were women and 32% men. The occurrence of bruises

corresponded to 38% after treatment A and 20% after treatment B (p=0.00). There was no significant difference between the average size of the bruise after both treatments (treatment A or B) (p=0.83). This study has many strengths: patients treated with oral anticoagulants or antiplatelet drugs were excluded; subjects had not received heparin in the days preceding the study; the order of treatment (A or B) was randomly selected; patients' abdominal skin integrity was evaluated before their inclusion in the study; besides the high level of standardization of the procedure and the injection administration by expert nurses.

In general, these studies revealed methodological limitations, such as the lack of standardization of the procedure, sample size and homogeneity. Nevertheless, they contribute to the planning of further research aimed at performing the procedure based on scientific evidence.

4 Discussion

In this integrative review, eight studies were selected that assessed LMWH administration techniques to reduce adverse outcomes like hematomas, bruising and local pain. Almost all papers were published in nursing journals, showing that knowledge production about the SC administration of LMWH arouses great interest and concern in this professional category. Hematomas, bruising and pain do not only cause stress in patients, especially those submitted to long-term LMWH therapy, but often make the site unfeasible for the future administration of other SC drugs [5, 6].

Most studies showed experimental and quasi-experimental designs, resulting in publications of good quality. Although experimental studies represent the gold standard to assess the cause-and-effect relation between intervention and outcome, this design is not possible sometimes. In these cases, quasi-experimental designs are used to assess the effectiveness of nursing interventions. The lack of random group allocation and the exposure of both groups to the pre and post-test may not be ideal from an academic perspective. In clinical practice, however, this is often the only feasible design, which may explain its adoption in most publications. In addition, the findings related to the study design demonstrate nurses' investment in the comparison of techniques that guarantee the correct absorption of the drug, reduce adverse reactions and guarantee greater comfort and safety to the patients [24].

As regards the LMWH administration technique, the best evidence available suggests that an application time of 30 s, when compared to 10 s, reduced the incidence of adverse outcomes [6, 9, 22]. The incidence and extent of the bruising was greater in the 10 s than in the 30 s technique. These findings clearly indicate that slow LMWH injections decrease the probability of the appearance of this reaction [6, 9, 21, 22].

In patients with an LMWH application time of 30 s, pain intensity dropped by 32.5% [21] to 50% [6]. In other studies [12, 24], the pain was not correlated with the administration time. In nursing textbooks [25, 26] and specialized databases, no recommendations are provided regarding the administration time [27]. In the literature, it is recommended that LMWH injections be applied slowly, but without describing the time. Rapid injections can cause pain due to the increased tissue pressure the drug volume causes [28]. One possible explanation is that more time is needed for the SC tissue to accommodate the injected volume, thus reducing the tissue pressure and pain intensity in the puncture site [6, 28]. In addition, slow injections seem to reduce the individuals' perceived pain, enhancing comfort during therapy [28].

The timeframe for the assessment of bruising and hematomas in the studies varied between 12h and 72h. Bruising usually takes place at 48 h (incidence peak) and tends towards resolution at 72 h after the use of LMWH [29], revealing that the assessment timeframe was appropriate in all studies. In only one research [20], the outcomes were analyzed during 10 days or until the end of the treatment. In that study, patients with a treatment time of more than five days showed higher incidence levels of hematomas and bruising (p<0.01). This finding is expected, as more punctures can predispose to a larger number of injuries, especially in cardiac patients hospitalized at intensive care units.

In three studies [6, 12, 21], a visual analogue scale (VAS) was used for pain assessment purposes, improving the precise measurement of this adverse outcome. The lack of objective pain assessment instruments can represent a weakness in the other studies.

Considering the needle length and caliber, no inferences can be made. Many authors did not inform these data in the research protocols [6, 20, 21-23] and only one analyzed this independent variable in bruising, hematomas and perceived pain. In that study, the authors concluded that there was no difference between the groups (30 G, 5/16" inch needle versus 26 G, 3/8" inch needle) in the development of hematomas (p=0.68) and mean pain scores (p=0.35). Despite the lack of evidences, the literature suggests that smaller-caliber needles (25-27 G) are the most indicated to reduce the occurrence of hematomas, bruising and pain in the application site of LMWH [5, 6, 30].

Concerning the type of syringe, half of the studies used prefilled syringes [6, 9, 22, 23]; one of them [20] compared prefilled (2ml) and non-prefilled syringes (2ml) with an air bubble regarding local adverse outcomes. In that study, with an LMWH treatment time of ten days, the group that received LMWH through a prefilled syringe, with or without aspiration, showed lower levels of bruising (p<0.048). In addition, the literature appoints that the advantage of using prefilled syringes is their lesser manipulation [29]. Incidence levels of bruising and hematomas were higher in women over 60 years of age (p<0.05) and obese individuals (p<0.01) [20].

The air bubble in the heparin syringe is aimed at promoting hemostasis in the SC injection site [20]. The presence or absence of this variable was not analyzed in any study as a factor that reduced or increased bruising, hematomas or pain. The presence of the bubble was recommended in non-prefilled [9, 20] as well as prefilled syringes [6].

The lifting of a skinfold and the 90º application angle have been well documented in the literature [5, 6, 12, 20, 21, 23], independently of what drug is administered. The lifting of the skinfold is aimed at raising the subcutaneous tissue to increase the distance from the underlying muscle, especially in thin patients [23]. Some authors described this practice as part of the technique [6, 20, 22, 23]. One of them [23] analyzed the presence or absence of the skinfold in the occurrence of hematomas in patients hospitalized at a trauma and orthopedics unit. In obese patients, the lifting of the skinfold represented a risk factor for the appearance of hematomas (p<0.001), while it served as a protection factor for non-obese individuals (p<0.001). A thick fat layer can hamper the drug administration in the SC tissue. On the other hand, in non-obese patients, the absence of the fold increases the risk of intramuscular injection [23].

All publications agreed on the abdomen as the preferred site for LMWH injection. The abdominal region holds a thicker subcutaneous tissue layer, an aspect that can minimize the risk of extravasation of the LMWH injection to the superficial tissue [31]. In addition, the large abdominal wall area can receive more injections [6]. Some care is essential though, like the maintenance of a five-centimeter distance from the umbilical scar to preserve the umbilical vein, as well as the avoidance of injections in scars or bruised areas [5].

In most protocols, the researchers did not include previous aspiration in the technique [6, 9, 12, 21-23]. One study analyzed the influence of aspiration on bruising and/or hematomas, concluding that no significant difference existed in the appearance of adverse events [20]. In an earlier publication, aspiration after inserting the needle into the subcutaneous tissue had already been considered unnecessary, indicating that the perforation of a blood vessel in this type of injection is rare [32]. In addition, aspiration promotes the movement of the needle inside the tissue, furthering the appearance of lesions like hematomas [7, 20].

5 Conclusions

In view of the research findings, the available evidence suggests high incidence levels of hematomas, bruising and pain in patients submitted to subcutaneous injections of LMWH. The administration technique the nursing team uses, involving

the use of a subcutaneous fold, no previous aspiration, use of prefilled needles, 90º angle to introduce the needle, slow injection (30 s), can result in less local trauma, with lower frequencies of adverse outcomes.

These findings are clinically important for nursing practices, as they can help in the elaboration of evidence-based care protocols and contribute to improve the quality of patient care delivery.

Implications for clinical practice

Today, variations in clinical nursing practice can no longer be attributed to a lack of scientific evidence, even if much evidence results from studies with low evidence levels. Hence, scientifically unfounded conducts are increasingly disqualified, although they still exist at many health services. The findings in this review permit outlining some recommendations regarding subcutaneous administration of LMWH, which are: use of prefilled syringes with an air bubble; use of a 90º angle; use of skinfold in non-obese patients; administration in the abdominal region; no use of previous administration; slow injection of the solution (30 s) and without massaging.

Conflict of interest

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