


Effect of Cold Application on Pain and Bruising in Patients With Subcutaneous Injection of Low-Molecular-Weight Heparin: A Meta-Analysis

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Haifeng Wang, BA¹ , Jingjing Guan, MD¹, Xiaohan Zhang, MD¹,
Xinxin Wang, MD¹, Tianliang Ji, MD¹, Dandan Hou, MD²,
Guiru Wang, BA¹ , and Jiao Sun, PhD³

Abstract

To evaluate the effect of cold application on pain and bruising after the subcutaneous injection of low-molecular-weight heparin, 8 electronic databases were searched for randomized controlled trials and quasiexperimental studies from the inception of the databases to June 2019. Review Manager 5.3 software was used for the heterogeneity test and meta-analysis. A total of 8 studies including 694 participants were analyzed. The cold application group assessed with the Verbal Descriptor Scale pain assessment tool showed significant reductions in pain intensity immediately after injection. Compared to the control group, the cold application group showed a reduction in the occurrence of bruises at 12 hours, 24 hours, and 48 hours after injection. There was no significant difference in the area of bruising in the cold application group at 48 hours after injection, but the area of bruising at 72 hours after injection was significantly reduced. These results show that cold application can reduce the incidence of pain and bruising after subcutaneous injection of low-molecular-weight heparin and reduce the area of bruising 72 hours after injection. Additional studies with larger sample sizes are needed to confirm these findings.

Keywords

low-molecular-weight heparin, injections, subcutaneous, cold application, pain management, bruising

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Introduction

Heparin is an anticoagulant used in the surgical prevention of thrombosis, and it can quickly achieve anticoagulant effects and prevent and treat venous thrombosis.¹⁻³ Low-molecular-weight heparin (LMWH) is prepared by depolymerization of the common form of heparin. Low-molecular-weight heparin is a relatively new anticoagulant that was developed in the 1970s.⁴ Compared to heparin, LMWH has the advantages of high bioavailability, a strong antithrombotic effect, and fewer bleeding side effects.^{5,6} Therefore, LMWH is increasingly widely used in clinical practice.

The main method of administration of LMWH is subcutaneous injection in the abdomen, inferior edge of the deltoid muscle on the upper arm or lateral thigh.⁷ This method of administration often causes side effects, including pain at the injection site, bruises, sclerosis, and the occurrence of hematomas.⁸ It has been reported that the incidence rates of bruises and hematomas after the subcutaneous injection of LMWH is

26.6% to 88.9% and 40% to 88%, respectively.⁹ These side effects often negatively affect the patient, leading to anxiety, a loss of confidence, and even the refusal to be treated, which may also endanger the safety of the patient.^{7,10} In addition, after bruising, it is necessary to avoid repeated injections in the bruised area, thus limiting the injectable areas. Therefore,

¹ Urology department, The First Hospital of Jilin University, Changchun, China

² Nursing department, The First affiliated Hospital of Zhengzhou University, Zhengzhou, Henan, China

³ School of Nursing, Jilin University, Changchun, China

Corresponding Authors:

Guiru Wang, Department of Nursing, Physical Examination Center, The First Hospital of Jilin University, Changchun, China.

Emails: wgrw555@sohu.com; wgr61656@126.com

Jiao Sun, School of Nursing, The First Hospital of Jilin University, Jilin University, Changchun, China.

Email: sunjiao@jlu.edu.cn



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when nurses perform subcutaneous injections of LMWH, they should use techniques and methods that minimize the incidence of the abovementioned adverse consequences to improve patients' satisfaction with the quality of the nursing they receive, enhance their trust in health-care providers, and encourage them to cooperate with treatment.

At present, the factors affecting pain and bruising caused by the subcutaneous injection of LMWH include the injection time,^{11,12} the injection site,⁷ the injected dose,¹³ the needle size,¹⁴ and the application of cold therapy. Cold application is a treatment that reduces tissue temperature, blood flow, and cell metabolism.¹⁵ Cold application, a nondrug intervention, can help reduce the severity of pain by reducing catecholamine levels, increasing endorphin levels, and delaying the transmission of pain signals to the central nervous system.¹⁶⁻¹⁸ Cold application can also contract peripheral blood vessels and reduce the flow of blood to the tissue, thereby reducing the occurrence of bruises and hematomas.^{18,19}

However, the effect of cold application on reducing pain and bruising induced by the subcutaneous injection of LMWH is controversial. In some studies,²⁰ there was no significant difference between the cold treatment group and the control group in terms of the pain at the injection site, while other studies²¹⁻²³ showed the opposite result. Some researchers²³ also showed that there were no significant differences in the occurrence and size of bruises between the cold application group and the control group, but the results of most studies showed that there were significant differences between the 2 groups. Due to the variability among studies, there is no clear, final conclusion regarding the effect of cold application on the reduction of pain and bruising after LMWH injection, and no meta-analysis has explored this problem. Therefore, the purpose of this article was to review this controversial issue and to evaluate the effect of cold application on pain and bruising after the subcutaneous injection of LMWH.

Methods

This review was conducted in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA). The data used in this meta-analysis were from previously published studies; therefore, ethics approval and patient informed consent were not necessary.

Inclusion and Exclusion Criteria

The 2 independent review authors (H.W. and X.Z.) screened and selected all studies. We determined the inclusion criteria for the study based on PICOS, and the specific inclusion criteria are as follows:

1. **P** (Participants). Patients older than 18 years of age who received a subcutaneous abdominal LMWH injection in a hospital or clinic did not use other anticoagulant drugs during treatment, did not have any conditions that could induce bleeding, did not have liver or renal

insufficiency, and did not receive any other drugs (such as insulin) via injection at the injection site.

2. **I** (Intervention). Cold was applied for 2 to 20 minutes before and after the subcutaneous injection of LMWH.
3. **C** (Control). A control group received the injection with the same technique used in the intervention group without cold application before or after the injection.
4. **O** (Outcomes). The outcomes were pain intensity, the occurrence of bruises, and the size of the bruise at the injection site (diameter and area of the bruise).
5. **S** (Study design). Randomized controlled trials (RCTs) and nonrandomized experimental studies were included.

Search Strategy

To identify relevant studies, we searched the following 8 databases for all articles from the inception of the database to June 2019: PubMed, Web of Science, Embase, the Cochrane Library, CINAHL, the Wanfang Database, the China National Knowledge Infrastructure, and Sinomed. For the specific retrieval strategies, see Online Appendix 1. We also manually searched the references of the identified articles to find additional potentially relevant research articles.

We used Endnote 7 to remove all duplicate studies. The references of the potentially relevant studies were examined to identify any additional studies that met the inclusion criteria that might have been missed by the database searches. The titles and abstracts of the studies retrieved from the databases and other sources were independently screened by the 2 authors (H.W. and X.Z.) to determine whether they met the abovementioned inclusion criteria. We downloaded the full texts of possibly eligible studies, and the full-text articles were independently evaluated by the same 2 authors (H.W. and X.Z.) on the basis of the inclusion criteria. Disagreements between the 2 authors were resolved through discussion with a third author (G.W. or J.S.).

Data Extraction

The 2 authors (H.W. and X.Z.) used a predesigned data collection form (Microsoft Office Excel) to independently extract the data from the included studies. If there was a disagreement, it was discussed with a third author (G.W. or J.S.). We collected the following data from the included studies: lead author, year of publication, country, study design (randomization, allocation, and blinding methods in RCTs), subjects, participant characteristics, sample size, main inclusion and exclusion criteria, intervention methods and duration, injection site, injection drug, injection dose, methods of measuring pain and bruises, and results.

Quality Assessment

The 2 authors (H.W. and X.Z.) independently assessed the methodological quality and risk of bias due to the selective inclusion of studies, and disagreements were resolved by

discussion with a third author (G.W. or J.S.). We evaluated the RCTs (using the Checklist for RCTs) and nonrandomized experimental studies (using the Checklist for Nonrandomized Experimental Studies) using The Joanna Briggs Institute (JBI) Critical Appraisal Tools. The risk assessment table for RCTs includes 13 topics, such as randomization, allocation concealment, baseline level consistency, blinding method, and treatment consistency. The risk assessment table for nonrandomized experimental studies includes 9 topics, such as variable confusion, participant characteristics, result measurements, and statistical analysis methods. The risk assessment tool website is <https://joannabriggs.org/research/critical-appraisal-tools.html>.

Statistical Methods

We used the Review Manager version 5.3 software developed by the Cochrane Collaboration for the heterogeneity test and meta-analysis, and two authors (H.W. and X.Z.) entered the data. Before pooling the results, we calculated the I^2 statistic to determine the statistical heterogeneity of the studies. When the heterogeneity was low ($I^2 < 50\%$), a fixed effects model was used to combine the results, and when the heterogeneity was high ($I^2 \geq 50\%$), a random effects model was used. The dichotomous variables were assessed by the odds ratio (OR), the continuous variables with the same units were assessed by the mean difference (MD), and the continuous variables with different units were assessed by the standardized mean difference (SMD) effect index. A 2-sided P value $< .05$ indicated statistical significance. We collected data across different time points, so the number of studies and number of participants were small at each point in time.

Results

Literature Search Results

A total of 693 studies were obtained from the databases, and 1 related study was obtained from the references of those studies. After the titles and abstracts were screened, 674 studies were excluded because they either were duplicates (125 studies) or did not meet the inclusion criteria (549 studies). Then, we read the full texts of the 20 studies, 12 of which were excluded: 7 studies were registrations of controlled trials, 2 studies were not in English,^{24,25} 1 study had no specific data,²⁶ and 2 studies involved injections in the arm and not in the abdomen.^{19,27} Finally, a total of 8 studies were included in this study.^{20-23,28-31} The study selection process is further summarized in the PRISMA flow diagram in Figure 1.

Characteristics of the Included Studies

This review included 8 studies that were conducted in Iran, Turkey, and China and published between 2001 and 2019. Four studies were published in English, and the other 4 studies were published in Chinese. Five studies were RCTs, and 3 studies were nonrandomized experimental studies. The intervention group was treated with cold application for 2 to 20 minutes

before and after injection, while the control group was given a routine injection without cold application. A total of 694 participants were included in the 8 studies: 4 studies^{22,23,29,30} injected enoxaparin at doses of 0.6 mL, 0.4 mL, 4500 IU, and 0.2 mL; 2 studies^{21,28} injected LMWH calcium at doses of 0.1 mL/kg and 4100 IU; and another 2 studies did not mention the specific drugs injected. We considered that the intensity of pain and the size of the bruise caused by injection into the arm, thigh, and abdomen might be different, so we only included studies involving injection into the abdomen. Four studies^{20,22,23,29} divided the participants into multiple intervention groups; for example, the study by Amaniyan et al randomly divided participants into 3 groups: intervention group 1 was treated with cold application for 20 minutes, intervention group 2 was treated with cold application for 20 minutes first and with hot application for 20 minutes after 12 hours, and the control group was only given a routine injection without cold or hot application. In accordance with the purpose of this review, we only selected the data of the cold application group and control group for analysis. One study²² used a self-controlled design, using cold application on one side of the abdomen and not on the other side. Table 1 summarizes the characteristics of the studies.

Risk of Bias in the Included Studies

We used the JBI Critical Appraisal Checklist to assess the risk of bias in the RCTs and nonrandomized experimental studies (see Tables 2 and 3). Five studies were described as “randomized,” but only 3 studies reported the randomization methods they used. Only 1 study described the allocation concealment and blinding of assessors but did not report the blinding methods for the participants or the researchers. The 8 studies that were included reported that there was no significant difference in age, sex, or other demographic information between the cold application group and the control group at the baseline level ($P > .05$).

Meta-Analysis Results

Pain Intensity

A total of 4 studies²⁰⁻²³ evaluated pain intensity after the subcutaneous injection of LMWH. One of the studies²⁰ assessed pain intensity immediately, 48 hours, 60 hours, and 72 hours after injection, while the other 3 only assessed pain immediately after injection. Two studies^{22,23} used the Verbal Descriptor Scale (VDS) for the assessment of pain, and the other 2 studies^{20,21} used the Visual Analogue Scale (VAS). Therefore, meta-analysis was carried out separately.

The meta-analysis of the 2 studies using the VDS for the assessment of pain (Figure 2A) showed that compared to the control group, the cold application group had a significantly lower pain intensity immediately after injection (OR: 0.28, 95% confidence interval [CI]:0.11-0.69, $I^2 = 57\%$, $P = .005$). The meta-analysis of the 2 studies using the VAS for the assessment of pain (Figure 2B) showed that there was no

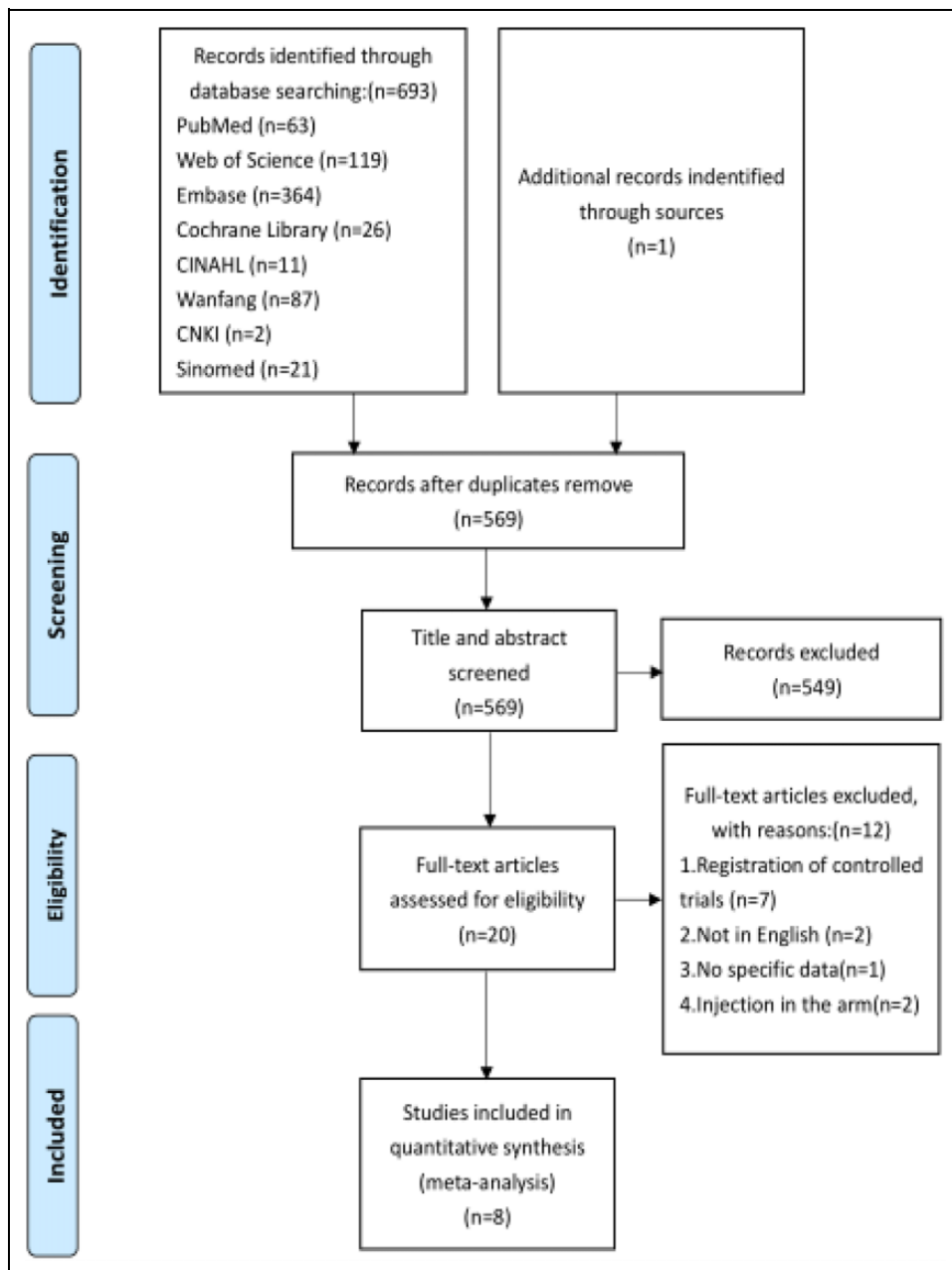


Figure 1. Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) flow diagram.

significant difference in pain intensity between the cold application group and the control group immediately after injection (MD: -0.94 , 95% CI: -3.13 to 1.26 , $I^2 = 88\%$, $P = .40$).

The Occurrence of Bruising

Eight studies evaluated the occurrence of bruising after the subcutaneous injection of LMWH. Among these studies, 4 studies^{21,28,30,31} evaluated the occurrence of bruising 12 hours after the injection. The level of heterogeneity of these results was very high. Therefore, we used a random effects method to pool the results of the studies, and the difference was statistically significant (OR: 0.18 , 95% CI: 0.06 - 0.52 , $I^2 = 89\%$, $P = .001$). Four

studies^{20,22,23,29} evaluated bruising 48 hours after injection. The results of the meta-analysis showed that the occurrence of bruising in the cold application group was lower than that in the control group (OR: 0.26 , 95% CI: 0.08 - 0.62 , $I^2 = 73\%$, $P = .02$). The heterogeneity of bruising 72 hours after injection was high, and there was no significant difference (OR: 0.08 , 95% CI: 0.01 - 1.01 , $I^2 = 86\%$, $P = .05$; see Figure 2). Meta-analysis of pain intensity is shown in Figure 3.

Size of Bruises

Bruising diameter. Two studies^{29,31} measured the diameter of the bruises after the subcutaneous injection of LMWH; the results

Table 1. Characteristics of the Included Studies.

Author (Year/Country)	Study Design	Participant Setting	Age, M ± SD	Sample Size (E/C)	Injection Protocol	Intervention			Outcome
						Cold Application Group (E)	Control Group (C)		
Hu (2019/China)	RCT	Patients who were hospitalized with transient ischemic attacks	55.04 ± 7.87	89 (45/44)	Quick injection; pressing for 10 minutes after pulling out the needle; low-molecular-weight heparin calcium 0.1 mL/kg, every 12 h	After injection, the ice bag is placed for 5 minutes	Received routine hospital care, no ice bag placed	a+b	
Men et al (2017/China)	Nonrandomized experimental study	Patients who were hospitalized with transient ischemic attacks	59.78 ± 10.26	60 (30/30)	Insertion angle 90°; pressing for 5-15 minutes after pulling out the needle; low-molecular-weight heparin calcium (Fraxiparine) 4100 IU, every 12 h	After injection, the ice bag is placed for 5 minutes	Received routine hospital care, no ice bag placed	b	
Amaniyan et al (2016/Iran)	RCT	Patients who were hospitalized with coronary disease	59.56 ± 1.81	120 (60/60)	27-gauge syringes; insertion angle 90°; injection without drug aspiration; 30 seconds of injection; enoxaparin sodium injections (60 mg/0.6 mL) twice a day	A reusable cold gel pack, covered with a fabric towel bag, was applied to the injection site for 20 minutes immediately after each injection	Patients in this group did not receive any special intervention beyond that of the routine injection of subcutaneous enoxaparin sodium	b+c	
Wang et al (2012/China)	RCT	Patients who were hospitalized with acute coronary syndrome	61.4	98 (49/49)	Insertion angle 90°; pinching at injection site; slow injection; pressing for 5 minutes after pulling out the needle; LMWH 5000 IU, every 12 h	After injection, an ice cube was applied to the injection site for 10-15 minutes	Received routine hospital care, no ice cubes placed	b+d	
Kuzu and Ucar (2001/Turkey)	Non-randomized experimental study	Patients who were hospitalized at Hacettepe University Hospital Orthopaedics and Internal Medicine Services	Unclear	32 (15/17)	Insertion angle 90°; pinching at injection site; injection without drug aspiration; 1.25-cm long needle; applying a light pressure at the injection site after the injection and not massaging the site; 20 mg (0.2 mL) enoxaparin twice a day	Cold packs were used before and after injection for 5 minutes	Cold was not applied	a+b+c+e	

Abbreviations: a, pain intensity; b, incidence of bruising; c, size of bruising; d, bruising diameter; e, pain duration; LMWH, Low-molecular-weight heparin; RCT, randomized controlled trials; SD, standard deviation.

Table 2. Risk of Bias in the Randomized Control Trials.

	Hu (2019)	Amaniyan et al (2016)	Sendir et al (2015)	Liang et al (2015)	Wang et al (2012)
1. True randomization	Y	U	Y	Y	U
2. Allocation concealment	U	Y	U	U	U
3. Similar at baseline	Y	Y	Y	Y	Y
4. Blinding of participants	N	U	U	U	U
5. Blinding of researchers	N	U	N	N	U
6. Blinding of assessors	N	Y	U	N	U
7. Identical treatment other than intervention	Y	Y	Y	Y	Y
8. Follow-up description	Y	Y	N	Y	Y
9. Intention-to-analysis	Y	Y	N	Y	Y
10. The same outcome measurement	Y	Y	Y	Y	Y
11. Reliability of outcome measurements	U	U	U	U	U
12. Appropriate statistical analysis	Y	Y	Y	Y	Y
13. Appropriate trial design	U	U	U	U	U

Abbreviations: Y, yes; N, no; U, unclear.

Table 3. Risk of Bias in the Nonrandomized Experimental Studies.

	Men et al (2017)	Avsar and Kasikci (2013)	Kuzu and Ucar (2001)
1. Clear cause and effect	NA	NA	NA
2. Similar comparisons	Y	Y	Y
3. Similar treatment other than intervention	Y	Y	Y
4. Control group	Y	Y	Y
5. Multiple measurements	U	U	U
6. Follow-up description	Y	Y	Y
7. The same outcome measurement	Y	Y	Y
8. Reliability of outcome measurements	Y	Y	Y
9. Appropriate statistical analysis	Y	Y	Y

Abbreviations: Y, yes; N, no; U, unclear; NA, not applicable.

were recorded in centimeters or millimeters, but the time points of the measurements in the 2 studies were different, so the data could not be pooled. One study³¹ measured the bruising diameter 12 hours after the injection and found that the bruising diameter in the cold application group was significantly smaller than that in the control group (SMD: -4.24 , 95% CI: -4.97 to 3.52 , $P < .001$). Another study²⁹ measured the diameter of bruising 24 hours (SMD: -5.80 , 95% CI: -6.62 to 4.97 , $P < .001$), 48 hours (SMD: -8.24 , 95% CI: -9.36 to 7.12 , $P < .001$), and 72 hours after the injection (SMD: -12.24 , 95% CI: -13.86 to 10.63 , $P < .001$). Compared to the control group, the diameter of bruising in the cold application group was significantly smaller than that in the control group. The difference was statistically significant.

Bruising area. Three studies^{20,22,23} measured the area of the bruise after the subcutaneous injection of LMWH. The results were recorded in square millimeters. All 3 studies measured the area of the bruise 48 hours and 72 hours after injection as shown in Figure 4; there was no significant difference in the

area of the bruise between the cold application group and the control group 48 hours after the injection (MD: -2.47 , 95% CI: -5.73 to 0.78 , $I^2 = 89%$, $P = .14$), while the area of the bruise 72 hours after the injection was significantly smaller in the cold application group than in the control group (MD: -3.91 , 95% CI: -6.16 to 1.66 , $I^2 = 75%$, $P < .001$); the degree of heterogeneity was high.

Discussion

Low-molecular-weight heparin is a commonly used anticoagulant that has a certain inhibitory effect on blood coagulation.³² Therefore, the subcutaneous injection of this drug can easily cause bruising and pain at the injection site. To alleviate the negative effects experienced by patients, it is the responsibility of health-care workers to take measures to reduce bruising and pain. In theory, cold application can reduce blood flow and nerve conduction velocity,^{33,34} thus reducing bruising and pain intensity; this method is considered to be an effective measure, but the results of some research studies contradict this theory, resulting in the absence of a unified conclusion on this issue. In this article, the effects of cold application on pain and bruising after the subcutaneous injection of LMWH were reviewed.

Summary of the Main Results

Considering the shortage of data included in RCTs alone, we also included nonrandomized experimental studies to increase the amount of data available. Finally, 5 RCTs and 3 nonrandomized experimental studies met our inclusion criteria. The intervention group was treated with cold application before or after the subcutaneous injection of LMWH, while the control group received the same injection method as the intervention group but did not receive cold application. All the studies involved injections into the abdomen, and a total of 694 participants were included in the analysis of the effects of cold application on pain and bruising after the subcutaneous injection of LMWH.

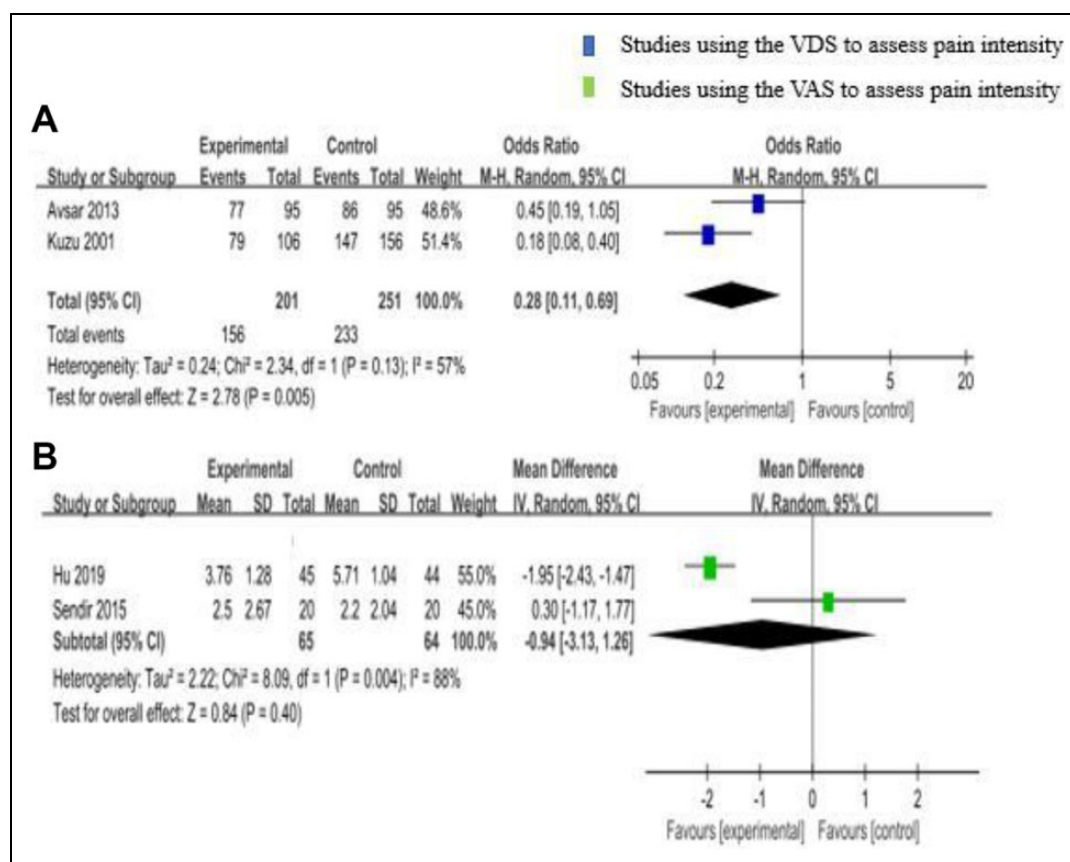


Figure 2. Meta-analysis of pain intensity.

The meta-analysis showed that, compared to the control group, the cold application group did not have reduced pain intensity immediately after injection when the VAS was used to assess pain but did when the VDS was used. The Melzack theory can explain the analgesic effect of cold application: The local cold effect stimulates the mechanical receptors in the skin, helps prevent the transmission of pain to the T cells, and stimulates glial cells to prevent the feeling of pain.^{35,36} However, because the VDS score is a dichotomous variable and the VAS score is a continuous variable, the data could not be combined, resulting in a small sample size in each group, which greatly affected the results of the study. For example, in Sendir et al's study,²⁰ the pain score of the cold application group was significantly higher than that of the control group immediately after injection, which may be the main reason for this result. Both scales have limitations. The VDS is not suitable for patients with low educational levels who cannot accurately describe the degree of pain, and the VAS is not suitable for elderly patients with visual impairments. Because the 2 scales have different inclusion groups, the selection of the scale is inconsistent, which is another factor affecting the results. Therefore, the following recommendations are made for future studies: include a uniform population, exclude patients with different needs, select appropriate scales for large-sample studies, and include both objective indicators,

such as pain duration and subjective indicators to improve credibility and persuasiveness.

The occurrence of bruising at the injection site was reduced 12 hours and 48 hours after injection in the cold application group compared to the control group. Compared to that in the control group, the bruising area at the injection site in the cold application group was not significantly affected 48 hours after the injection, but it was significantly reduced 72 hours after the injection. The main reason for these results is that cold application causes blood vessels at the injection site to constrict, increasing blood viscosity, slowing blood flow, and promoting blood clotting, thereby reducing the incidence and size of bruises.^{26,37} Bruises are defined as changes in skin color $\geq 2 \text{ mm}^2$, and changes in skin color $< 2 \text{ mm}^2$ are not considered bruises³⁸; bruises usually peak in size within 48 hours and begin to shrink 72 hours after formation.³⁹⁻⁴¹ However, in the data included in this study,²⁰ changes in skin color $< 2 \text{ mm}^2$ were included; these changes may be related to the different measurement time points and may be the reason cold application did not have any effect on the bruising area 48 hours after the injection. The second reason is the small sample size at each measurement time point. Future studies should increase the sample size, select important time points for the measurements, and adopt more rigorous clinical trial designs.

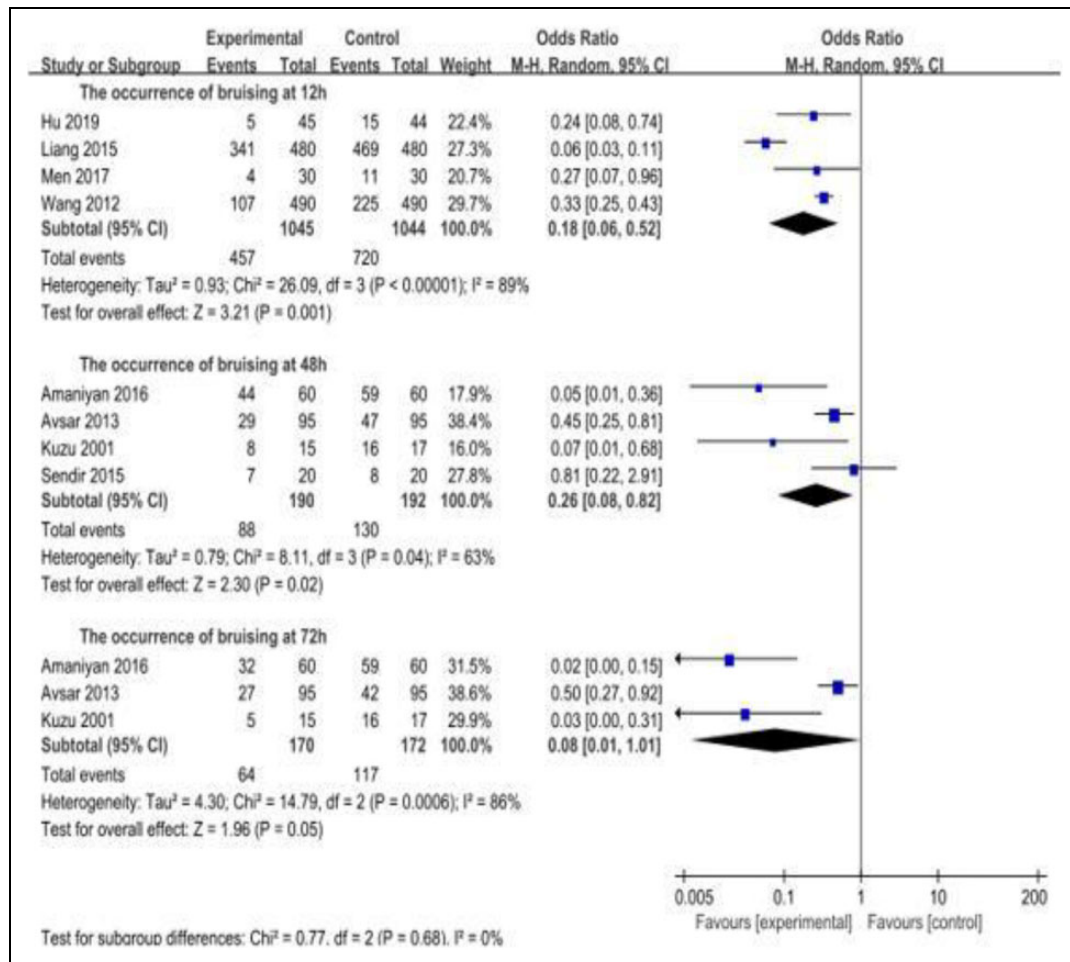


Figure 3. Meta-analysis of the occurrence of bruising.

Strengths and Limitations

This review has several advantages. First, this is the first review of the effect of cold application on pain and bruising after the subcutaneous injection of LMWH. The results show that cold application can reduce pain and bruising in patients, which provides some practical guidance for medical and nursing professionals in clinics. Second, we thought that the pain intensity and bruise size caused by injections in different sites (arm, thigh, and abdomen) might vary, so we excluded 2 studies involving injections in the arm, which increased the rigor of this study. This review has some limitations. First, in addition to RCTs, nonrandomized experimental studies were included in this study, which resulted in a low quality of the evidence in this study and may have affected the research results. Second, language limitations may have narrowed the scope of the study and affected the results of the pooled analysis. Third, the different diseases of the participants may have affected the results. Fourth, the use of analgesics was not mentioned in the included studies, and the use of analgesics has a substantial impact on pain intensity. Fifth, the researchers used different injection regimens, such as needle size, injection dose, injection time, and withdrawal time, all of which affect pain and bruising.

Sixth, data were collected at different time points, so the numbers of studies and participants were small for each time point.

Implications for Clinical Practice and Research

Although the number of participants in the study was small, the meta-analysis results showed that cold application can reduce pain intensity after the subcutaneous injection of LMWH (using the VDS), significantly reduce the occurrence of bruising, and reduce the bruising area 72 hours after the injection. In clinical practice, health-care workers can make full use of cold application to alleviate pain and bruising at the injection site and develop nursing practice guidelines based on evidence-based practices to reduce patients' pain and increase their confidence in the treatment they receive. Therefore, the results of this study have important clinical significance for nursing practice. However, future studies should include large sample sizes, adopt appropriate methods for randomization and blinding, use standardized techniques and measurements, evaluate results at similar times, consider other issues such as hematomas and induration at the injection site, and adopt rigorous trial designs to determine the best time for cold application, that is, the

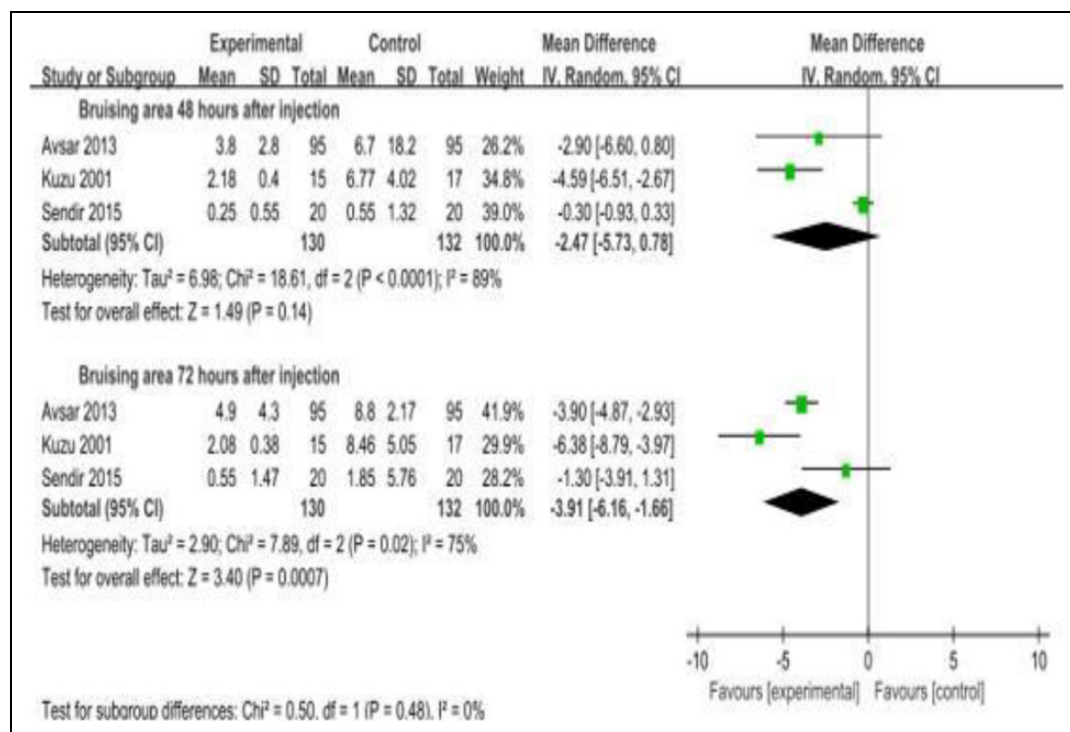


Figure 4. Meta-analysis of the area of the bruise.

application time that ensures reductions in pain and bruising, as well as reductions in the time requirements for nurses and health-care workers, thus satisfying the demands of both the patients and the medical staff.

Conclusions

This review is the first evidence-based analysis of the effects of cold application on pain and bruising following the subcutaneous injection of LMWH. The results showed that cold application could reduce pain intensity, bruising incidence, and bruising area 72 hours after the injection. Therefore, cold application as a clinical practice to reduce the side effects of the subcutaneous injection of LMWH is supported. However, due to the limitations of previous studies, including the small sample sizes at different time points and the low quality of the evidence, large, well-designed, prospective studies are needed to further confirm our findings.


Declaration of Conflicting Interests


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ORCID iD

Haifeng Wang  <https://orcid.org/0000-0002-6320-8883>

Guiru Wang  <https://orcid.org/0000-0002-7599-4543>

Supplemental Material

Supplemental material for this article is available online.

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