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Effects of Vapocoolant Spray Prior to SC LMWH Injection: An Experimental Study

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Abstract

The aim of this study was to evaluate the effects of vapocoolant spray administration prior to subcutaneous (SC) low molecular weight heparin injection on local ecchymosis, hematoma, and pain. This randomized controlled study was carried out on 64 patients ($n = 128$ injections) in an orthopedics and traumatology clinic. After randomization, vapocoolant spray and then heparin injection was applied on one arm. The second necessary dose of heparin was applied to his or her other arm as a placebo by a water spray. Then, the pain of the patients was assessed. After 2 days, ecchymosis and hematoma were evaluated. Significant lower pain scores were determined in applications in which the vapocoolant spray was used. There was no statically significant difference between the mean diameter values of ecchymosis in both arm groups. There was no hematoma on the injection site after injections. However, this method did not create any significant reductive effect on ecchymosis. Nurses are advised to take advantage of vapocoolant spray effects prior to SC heparin injection.

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Introduction

In orthopedic surgery, to avoid thrombosis and emboli, subcutaneous (SC) low molecular weight heparin (LMWH) injection is used once or twice a day as prophylaxis (Testroote, Stigter, Janssen, & Janzing, 2014; Zee, van Lieshout, van der Heide, Janssen, & Janzing, 2017). LMWH, which has many adverse effects on different systems, has common local adverse effects such as ecchymosis, hematoma, and pain (Zee et al., 2017). Ecchymosis, so-called bruises, is a result of leaking blood into the surrounding tissue after capillary injury in the injection site (Zaybak & Khorshid, 2008). Hematoma is a solid swelling within the tissue that can be palpated and is a result of the accumulation of clotted blood in the SC tissue. The frequency of ecchymosis is reported to be 42% to 90% in studies on patients using SC LMWH (De Campos, da Silva, Beck, Secoli, & Melo Lima, 2013; Nair, Kaur, & Sharma, 2008; Rızalar et al., 2007; Zaybak & Khorshid, 2008).

Another common adverse effect is pain at the injection site. Free nerve endings, freely found in superficial layers of the skin, cause acute pain during injection. Local pain, bruising, and deterioration of skin integrity may cause discomfort in patients (Avşar & Kaşikçi, 2013).

Bruising, hematoma, and pain due to injection are problems not only from the patients' perspective, but also for nursing interventions. Pain, ecchymosis, and hematoma may cause anxiety, deterioration in body image, limitations in the injection site, rejection of the treatment, and loss of the patient's confidence toward the nurse (Ciftci & Avsar, 2017; Rızalar et al., 2007). Therefore, nurses have an important role in sustaining safe medication management and minimizing potential adverse effects of medical treatment (Smeulers, Onderwater, van Zwieten & Vermeulen, 2014). These facts give additional responsibility to nurses to search out safe and standardized injection techniques to minimize unnecessary pain and potential complications (Avşar & Kaşikçi, 2013; Yi et al., 2016).

Background

There are various methods for a variety of factors to minimize ecchymosis, hematoma, and pain during SC LMWH reported in the literature (Avşar & Kaşikçi, 2013). Some of these methods include injection site selection (Ciftci & Avsar, 2017; Zeraatkari, Karimi, Shahrzad, & Changiz, 2005), changing

the needle (Klingman, 2000), practicing or not practicing aspiration, the air-lock technique (Avşar & Kaşikçi, 2013), length of injection duration (Akpınar & Çelebioğlu, 2008; Chan, 2001), time spent when the needle is in the SC tissue after medication administration (Akpınar & Çelebioğlu, 2008), and cold application (Amaniyan, Varaei, Vaismoradi, Haghani, & Sieloff, 2016; Kucukguclu & Okumus, 2010; Kuzu & Ucar, 2001).

Cold application is a simple and cheap nonpharmacological method used not only to improve injection technique, but also to decrease adverse effects. Cold application avoids pain sensation by affecting sensual nociceptors (Olive, Hollis, Mattson, & Topp, 2010; Ozveren, 2011). This method has been shown to decrease pain in acute soft tissue injuries (Olive et al., 2010; Perry, 2010). As a nonpharmacological intervention, local cold application prior to SC LMWH administration is shown to control bleeding, thus decreasing ecchymosis and hematoma by maintaining arteriolar vasoconstriction and increasing blood viscosity (Kucukguclu & Okumus, 2010; Kuzu & Ucar, 2001; Perry, 2010). Furthermore, cold application inhibits sending pain signals by gate control theory and diversion of attention to cold instead of pain (Avşar & Kaşikçi, 2013; Guyton & Hall, 2005).

Vapocoolant spray including chloroethyl used to prevent pain due to acute muscle injury is one of the nonpharmacological pain-control methods (Cohen et al., 2009). The spray immediately evaporates in seconds, decreases skin temperature, and maintains analgesia on the skin (Collado-Mesa, Net, Arheart, Klevos, & Yepes, 2015). It has been shown that this local intervention is safe and effective not only in adults but also in children (Boroumandfar, Khodaei, Abdeyazdan, & Maroufi, 2013; Cohen et al., 2009; Mace, 2016). Vapocoolant spray before vaccination was found to be an effective method in decreasing pain in children aged 4 years to 6 years by Cohen et al. (2009) and in adults by Mawhorter et al. (2004). In addition, vapocoolant spray before intravenous injection was found to decrease pain and to not show any side effects in adults by Fossum, Love, and April (2016). In the literature, there is no study on the effects of vapocoolant spray prior to SC LMWH administration in adults. There is a need for a study evaluating the effects of cold practice on pain, ecchymosis, and hematoma that can be achieved by vapocoolant spray instead of cold pack using a more standardized and practical approach.

Method

Aim

The aim of this study was to evaluate the effects of vapocoolant spray administration prior to SC LMWH injection on local ecchymosis, hematoma, and

pain. The hypothesis of this study is as follows: "compared to the results of the placebo group, vapocoolant spray administration prior to LMWH injection reduce ecchymosis, hematoma and pain on the injection site."

Study Design and Participants

This randomized controlled study was conducted in the orthopedics and traumatology clinic in a training and research hospital between December 2014 and May 2015 in Ankara, Turkey. The study sample consists of 64 patients who were hospitalized between the abovementioned dates, used SC LMWH, volunteered to participate in the study, were eligible for inclusion criteria, and were enrolled in a randomized approach by a random number table. Sample size was calculated using the literature (Amaniyan et al., 2016; Fossum et al., 2016; Mawhorter et al., 2004) and G-power program pack with the assistance of a statistician. The frequency of ecchymosis was assumed to be 40% on the arm on which cold spray was applied prior to injection and 60% on the arm on which cold spray was not applied; the difference between mean pain scores was assumed to be 0.6 cm on a 10-cm pain ruler with a standard deviation ± 1.5 cm. One hundred twenty-eight SC LMWH injections on 64 patients were estimated to be the sample with a 95% confidence interval and 80% power. A summary of the study process based on the CONSORT flow diagram (2010) is presented in Figure 1.

Inclusion criteria included being older than 18 years of age, undergoing surgical intervention for lower extremity, having a thrombocyte count more than 150,000/mm^3, not having a coagulation disorder, not having scar tissue, having an incision or a sign of infection on the injection site, not being allergic to cold, for each administration same dose LMWH prescribed patients, being communicable in Turkish, and volunteering to participate in the study (Figure 1).

Ethical Considerations

The study was approved by the clinical research ethics board at an authorized hospital affiliated with the Turkish Ministry of Health. Permission to perform the research was granted by the chief of the orthopedics and traumatology clinic in the study hospital. Written informed consent was obtained from each patient who met the inclusion criteria.

Intervention

In this clinical experimental study, the patients were themselves the control group. A random number table was used to select the patients to be

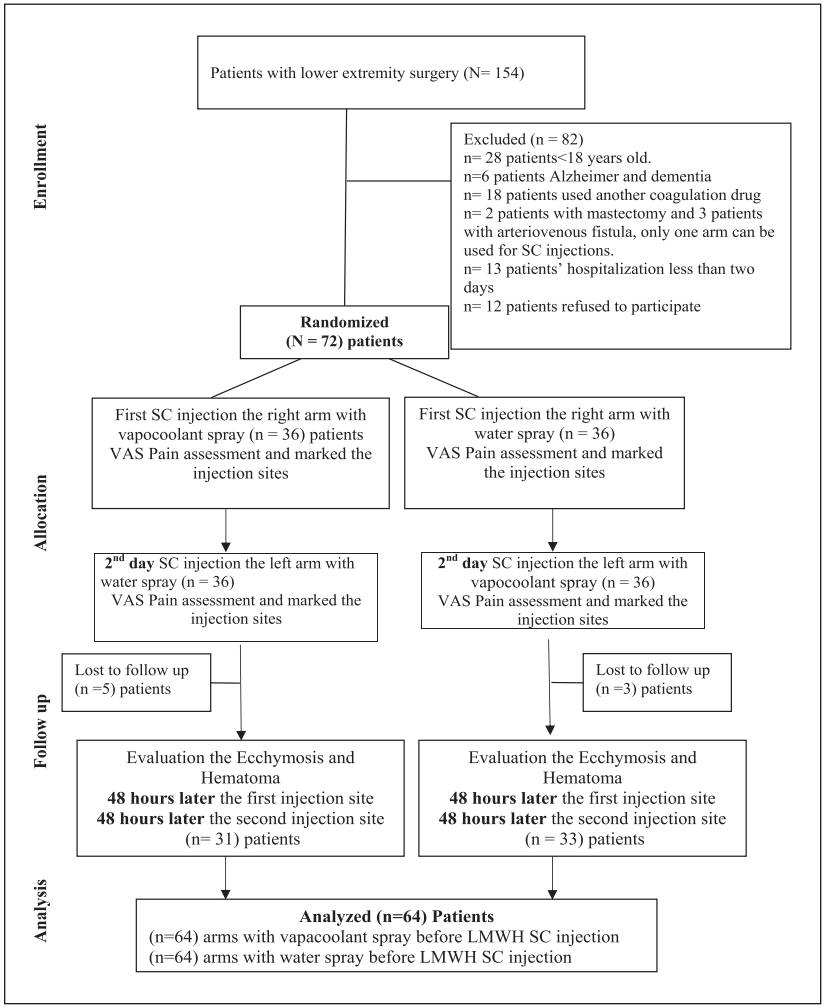

Figure 1. Study flow diagram.
Note. SC = subcutaneous; VAS = visual analog scale; LMWH = low molecular weight heparin.

enrolled in the study among the hospitalized patients. In our study, standard dose of LMWH was prescribed by the physician for all of our patients enrolled in the study till their discharge. One or two dose of 4,000 anti-Xa / 0.4 ml or 6,000 anti-Xa / 0.6 ml LMWH administration was ordered by the physician for the patients (Table 1). Same dose of LMWH injection

Table 1. Descriptive Characteristics of the Participants.

Characteristics	*n*(%)	*M* ± *SD*
Age (years)		45.65 ± 23.51
Gender		
Male	41 (64.1)	
Female	23 (35.9)	
Marital status		
Married	25 (39.1)	
Single	39 (60.9)	
Education status		
Primary school and less	39 (60.9)	
High school	15 (23.5)	
College and more	10 (15.6)	
Diagnosis		
Hip fracture	15 (23.4)	
Tibia, fibula fracture	12 (18.8)	
Gonarthrosis/coxarthrosis	11 (17.2)	
Lower extremity gunshot injury	7 (11.0)	
Ankle fracture	6 (9.4)	
Amputation	4 (6.3)	
Mass in lower extremity	4 (6.3)	
Calcaneus fracture	3 (4.7)	
Other	2 (3.1)	
Thrombocyte (mm^3)		280.95 ± 85.79
Additional chronic disease		
Yes	24 (37.5)	
No	40 (62.5)	
Low molecular weight heparin doze		
Enoxaparine sodium 4000 anti-Xa / 0.4 ml × 1/day	59 (92.2)	
Enoxaparine sodium 6000 anti-Xa / 0.6 ml × 1/day	3 (4.7)	
Enoxaparine sodium 6000 anti-Xa / 0.6 ml × 2/day	2 (3.1)	

was performed for each administration of each patient during their hospitalization period. To eliminate the confounding factor effect of dose, same dose of LMWH was administered to right and left arm. Also patients were control of themselves. Enrolled patients were allocated to the intervention group or the control group by a block randomization table. First, SC LMWH injection was performed on the right arm, and the second injection was performed on the next day on the left arm. However, in our clinic, the assessment of the injection area by the nurse and the choice of

Table 2. Comparison of Mean VAS Pain Score and Mean Diameter of Ecchymosis on Injection Site After SC LMWH.

Parameters	Groups: Water spray (placebo) $M \pm SD$	Groups: Vapocoolant spray (experimental) $M \pm SD$	Test (p)
VAS pain score	3.06 ± 2.08	2.37 ± 0.811	$z = 2.053$ $p = .040$*
Ecchymosis (cm)	1.24 ± 0.42	0.70 ± 0.611	$z = 1.592$ $p = .111$

Note. VAS = visual analog scale; SC = subcutaneous; LMWH = low molecular weight heparin; z = Mann–Whitney U test.
*$p < .05$.

Table 3. Comparison of Ecchymosis on Injection Site After SC LMWH Injections.

Groups	Ecchymosis: Yes	Ecchymosis: No	Test (p)
Water spray (placebo)	12	52	$\chi^2 = 0.948$
Vapocoolant spray (intervention)	8	56	$p = .330$

Note. SC = subcutaneous; LMWH = low molecular weight heparin.

patient are taken into account. In the routine practice, abdominal region is the primary and the lateral side of the arm is the secondary choice for LMWH injection due to thick SC tissue, less neurovascular elements, and less possible complications (ecchymosis, hematoma, and pain) in these sites (Avşar & Kaşikçi, 2013; Ciftci & Avsar, 2017; Ogston-Tuck, 2014). In our study, lateral side of the right and the left arm was chosen for SC injection for a few reasons such as (a) only two injections were to be assessed; (b) injections sites were far enough to make an easy comparison of ecchymosis, hematoma, and pain; (c) possible local side effects of vapocoolant spray that could spread on abdominal region was not foreseen by the researcher nurses; and (d) arms were far enough from routine injection sites (practitioner nurses were informed about the study so they would perform routine consecutive LMWH injections on the other possible injection sites as part of the treatment process). The appropriate injection site was selected, with exception to bruised, tender, hard,

swollen, inflamed, or scarred areas. In the intervention group, prior to SC LMWH injection, vapocoolant spray was performed for 10 s at a distance of 30 cm, and the site was cleansed with an antimicrobial swap after the next 10 s using a firm, circular motion while moving outward from the injection site. The area surrounding the injection site was grasped and bunched; then, the needle was injected at a 45° to 90° angle with the dominant hand. After the needle was placed, the tissue was released, the lower end of the syringe was steadied with the nondominant hand, and the injection was performed at a rate of 10 s/ml with the dominant hand. The needle was withdrawn quickly at the same angle at which it was inserted while supporting the surrounding tissue with the nondominant hand.

The tissue surrounding the injection site was marked at a diameter of 5 cm with a water-resistant pen. Patients were warned not to scratch or rub the injection site, while health care providers were informed not to administer any medication on the same injection site. The visual analog scale (VAS) was used to assess the pain. The next day, prior to SC LMWH injection, the water spray with identical packing was applied as a placebo on the other arm. The inspection for ecchymosis and hematoma was performed after 48 hr with a transparent measuring tool and noted on the inspection form. Patients were hospitalized postoperatively for a limited time (3-4 days) and the researchers needed at least 48 hr after the LMWH injections for a proper inspection so only first two postoperative injections were to be assessed in the study. Thirteen patients who were discharged or transferred to other clinics within 48 hr and whose skin inspection was not performed were excluded from the study (Figure 1). Both applications prior to injections and the SC LMWH injections were performed by the same nurse to avoid any variance. The skin inspection was performed by another nurse blinded to the intervention or control group.

Measures

Patient descriptive information form. The first part of the data collection form consisted of 17 questions on demographic characteristics, physical condition, and medical history of the patients.

VAS. The VAS is a commonly used assessment tool to evaluate variables ranging across a continuum of values such as acute pain severity (Breivik et al., 2008). Two extreme descriptions of the parameter are written on the two ends of a 100-mm line, and the patients are asked to mark where his or her state is on the line. For instance, “no pain” and “severe pain” can be written on the two ends of a line as extreme descriptions of the amount of pain felt

by the patients, and the patients are then asked to indicate his or her pain experience. The VAS score is determined by measuring the distance from no pain to the point that the patient has marked (Hjermstad et al., 2011). VAS is not a routine assessment tool used in our clinic for LMWH injections but a plastic ruler of 10 cm horizontal line on one side with verbal descriptors (word anchors) at each end on the other side was used by the researchers for study purposes.

Transparent measuring tool. Transparent measuring tool, which is a regular transparent plastic ruler, was used to measure the diameter of ecchymosis and hematoma. It is not a routine assessment tool used in our clinic but it was used by the researchers for study purposes.

Statistical Analyses

SPSS for Windows Version 22.00 (SPSS Inc., Chicago, IL, USA) Program Package was used for statistical analysis of the collected data. A normal distribution of the data was tested with the Shapiro–Wilk test. To present the descriptive statistics, the mean ± standard deviation (95% confidence interval) was used. Categorical variables were presented by number and percentage. In intergroup comparisons of continuous variables, the Mann–Whitney U Test (z) was used for nonnormally distributed variables. Pearson's chi square test (χ^2) was used for comparing categorical variables. $p \leq .05$ was accepted as significant.

Results

The study was completed with 128 SC LMWH injections on 64 patients. The mean age of the patients was 45.65 ± 23.51 years, 64.1% ($n = 41$) of them were male, 60.9% ($n = 39$) were single, and 60.9% ($n = 39$) were primary school graduates or less educated. The most common diagnoses in our participants were hip fracture (23.4%, $n = 15$) and tibia/fibula fracture (18.8%, $n = 12$). Mean platelet count was 280.95 ± 85.79/mm^3, and 62.5% ($n = 40$) of them did not have any additional chronic disease. Almost all of the patients (92.2%, $n = 59$) were prescribed Enoxaparin sodium 4000 anti-Xa / 0.4 ml × 1/day. Because each patient was in both intervention and control groups, there was no difference between groups (Table 1).

Regarding the comparison of pain according to VAS among patients using topical water spray and vapocoolant spray, after water spray, the mean pain score of patients was 3.06±2.08, and after vapocoolant spray, it was 2.37 ± 0.81; the difference was significant ($z = 2.053$, $p = .040$)

(Table 2). Regarding the assessment of ecchymosis on the injection site, ecchymosis was observed in 12 patients after water spray, while it was observed in 8 patients after vapocoolant spray, and there was no significant difference ($\chi^2 = 0.948$, $p = .330$) (Table 3). In comparison with the diameter of ecchymosis, after vapocoolant spray, the mean diameter of ecchymosis was 0.70 ± 0.611 cm, and after the placebo water spray was applied, the mean diameter of ecchymosis was 1.24 ± 0.42 cm; the difference between the mean diameters of ecchymosis was not significant (Table 2). There was no hematoma on the injection site in 64 patients after 128 injections. Temporary skin rash due to vapocoolant spray was observed in only four patients, and no allergic reaction or complications were observed.

Discussion

In our study, it was found that vapocoolant spray prior to SC LMWH was more effective in minimizing pain compared with the placebo (water spray), while the outcomes of the groups were similar in the means of hematoma and ecchymosis. There are no data on the outcomes of vapocoolant spray prior to SC LMWH in the literature, while administration of ice is reported to decrease pain (Avşar & Kaşikçi, 2013; Kuzu & Ucar, 2001; Varghese, Walia, Sharma, & Kaur, 2006). Furthermore, vapocoolant spray provides transient anesthesia via evaporative skin cooling, which suppresses pain receptor sensitivity and results in decreased pain perception. In addition, cold sensations transmitted via delta cold-specific fibers exert central gating on pain sensation transmitted via *C* fibers (Moon, Kim, & Choi, 2013). Because the pain relevant effect of vapocoolant spray became known, this approach has been used in immunization in children and adults, venous cannulation, and other medical interventions with needles (Cohen et al., 2009; Collado-Mesa et al., 2015; Fossum et al., 2016; Mace, 2016; Moon, Lee, & Kim, 2017). Fossum et al. (2016) has reported that vapocoolant spray is more effective compared with aerosol spray before venous catheterization for health care workers. Moon et al. (2017) has shown that vapocoolant spray had an effect on propofol-induced pain similar to the anesthetic effects of topical lidocaine. In addition, Collado-Mesa et al. (2015) has shown that vapocoolant spray prior to intradermal anesthetic injection in patients undergoing breast biopsy prompted decreased procedural pain and prevented negative experiences during intervention. Moon et al. (2013) had also shown that there was no significant difference in pain severity between vapocoolant spray and topical anesthetic ointment prior to needle electromyography examination.

Furthermore, it has been reported in a systematic review that vapocoolant spray administration prior to immunization in adults decreased pain (Shah et al., 2015).

Administration of ice is thought to have positive effects on ecchymosis and hematoma due to its physiological effects. The local physiological effect of ice is shown to decrease hemorrhage and blood flow by vasoconstriction and to decrease edema by decreasing metabolism, histamine discharge, and inflammatory processes (Amaniyan et al., 2016; Kucukguclu & Okumus, 2010; Moon et al., 2017). Moreover, it is a fact that cold achieves clotting by increasing the viscosity of blood and decreasing hemorrhage by contracting capillary surfaces (Guyton & Hall, 2005; Perry, 2010; Zaybak & Khorshid, 2008). However, it is known that it is impossible to completely eliminate ecchymosis by administering cold alone (Avşar & Kaşikçi, 2013). In our study, there was no hematoma in any of our patients, the mean number of ecchymoses observed and the mean diameter of ecchymosis were less than the data reported in the literature, and there was no significant difference between two groups. The reason for these findings may be the fact that none of our patients had clotting problems, and the platelet count number was above 150,000/mm^3 in all of them. Moreover, the possibility of ecchymosis and hematoma might have been minimized because all injections were performed by the same nurse with a standardized method in accordance with the clinical guidelines.

Despite the fact that there is no study on the effects of vapocoolant spray prior to SC LMWH administration on hematoma and ecchymosis, there are contradictory results in some studies on the effects of topical cold. Kuzu & Ucar (2001) reported no significant difference in hematoma and ecchymosis among patients who were administered cold before or after and both before and after SC LMWH injection in the control group. Kucukguclu and Okumus (2010) reported that the number of ecchymoses and the diameter of ecchymosis were smaller in patients who were administered ice packs before SC LMWH injection compared with the outcomes of the control group. Meanwhile, Avşar and Kaşikçi (2013) reported that the air-lock technique, not performing aspiration, and administering ice for 2 min decreased ecchymosis.

In our study, there were temporary rashes on the skin in four of our patients due to vapocoolant spray. Similar temporary and tolerable skin complications (rash, irritation, cold intolerance, and temporary skin-color changes) have been reported in studies on the effects of vapocoolant spray (Mace, 2016; Mawhorter et al., 2004; Shah et al. 2015).

Limitations

However our study has strong aspects, there are some limitations too. The enrollment of the patients undergoing lower limb surgery, comparison of only two administrations, only one injection site (lateral side of the arm), population of relatively young patients, patients not having coagulation problems and patients having a platelet count above 150,000/mm^3, as well as comparing only two groups, are the limitations of this study.

Conclusion

Safe and correct administration and injection methods for medications that will avoid negative outcomes on patients are important responsibilities of nurses. Optimal pain management interventions during injection should be effective, safe, and require minimal resources. Applying a vapocoolant spray is a method that fulfills these features and is currently being used in clinical practice for different purposes. This approach requires less time (approximately 20 s) to have positive effects compared with using a cold pack and is relatively inexpensive and easy to use.

Our study, which reveals the positive effect of vapocoolant spray on pain, has evidence-based value for nursing practice. Recognizing the positive effects of vapocoolant spray, including the decrease of pain, the number of ecchymoses, and the diameter of ecchymosis, we recommend using vapocoolant spray as a precaution before anticoagulation injection. We suggest that vapocoolant spray administration before SC LMWH should be investigated with larger sample sizes in patients with coagulation risk to find stronger evidence of its effects on ecchymosis and hematoma.

Declaration of Conflicting Interests

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References

Akpınar, R. B., & Çelebioğlu, A. (2008). Effect of injection duration on bruising associated with subcutaneous heparin: A quasi-experimental within-subject design. *International Journal of Nursing Studies*, *45*, 812-817.

Amaniyan, S., Varaei, S., Vaismoradi, M., Haghani, H., & Sieloff, C. (2016). Effect of local cold and hot pack on the bruising of enoxaparin sodium injection site: A randomized controlled trial. *Contemporary Nurse*, *52*(1), 30-41. doi:10.1080/10376178.2016.1190289

Avşar, G., & Kaşikçi, M. (2013). Assessment of four different methods in subcutaneous heparin applications with regard to causing bruise and pain. *International Journal of Nursing Practice*, *19*, 402-408.

Boroumandfar, K., Khodaei, F., Abdeyazdan, Z., & Maroufi, M. (2013). Comparison of vaccination related pain in infants who receive vapocoolant spray and breastfeeding during injection. *Iranian Journal of Nursing and Midwifery Research*, *18*(1), 33-37.

Breivik, H., Borchgrevink, P. C., Allen, S. M., Rosseland, L. A., Romundstad, L., Breivik Hals, E. K., . . . Stubhaug, A. (2008). Assessment of pain. *British Journal of Anaesthesia*, *101*(1), 17-24. doi:10.1093/bja/aen103

Chan, H. (2001). Effect of injection duration on site-pain intensity and bruising associated with subcutaneous heparin. *Journal of Advanced Nursing*, *35*, 882-892.

Ciftci, B., & Avsar, G. (2017). Assessment of three sites in terms of bruising in subcutaneous heparin administration. *International Journal of Caring Sciences*, *10*, 285-293.

Cohen, L. L., MacLaren, J. E., DeMore, M., Fortson, B., Friedman, A., & Lim, C. S. (2009). A randomized controlled trial of vapocoolant for pediatric immunization distress relief. *The Clinical Journal of Pain*, *25*, 490-494. doi:10.1097/AJP.0b013e3181a00414

Collado-Mesa, F., Net, J. M., Arheart, K., Klevos, G. A., & Yepes, M. M. (2015). Application of a topical vapocoolant spray decreases pain at the site of initial intradermal anaesthetic injection during ultrasound-guided breast needle biopsy. *Clinical Radiology*, *70*, 38-942. doi:10.1016/j.crad.2015.04.013

De Campos, J. D. F., da Silva, J. B., Beck, A. R. M., Secoli, S. R., & Melo Lima, M. H. (2013). Subcutaneous administration technique of low-molecular-weight heparins: An integrative review. *Clinical Nursing Studies*, *1*, 36-44. doi:10.5430/cns.v1n4p36

Fossum, K., Love, S. L., & April, M. D. (2016). Topical ethyl chloride to reduce pain associated with venous catheterization: A randomized crossover trial. *The American Journal of Emergency Medicine*, *34*, 845-850. doi:10.1016/j.ajem.2016.01.039

Guyton, A. C., & Hall, J. (2005). *Guyton and hall: Textbook of medical physiology* (11th ed.). Philadelphia, PA: Elsevier.

Hjermstad, M. J., Fayers, P. M., Haugen, D. F., Caraceni, A., Hanks, G. W., Loge, J. H., . . . European Palliative Care Research Collaborative. (2011). Studies comparing Numerical Rating Scales, Verbal Rating Scales, and Visual Analogue Scales for assessment of pain intensity in adults: A systematic literature review. *Journal of Pain and Symptom Management*, *41*, 1073-1093. doi:10.1016/j.jpainsymman.2010.08.016

Klingman, L. (2000). Effects of changing needles prior to administering heparin subcutaneously. *Heart & Lung*, *29*, 70-75.

Kucukguclu, O., & Okumus, H. (2010). The effects of the application of the ice to the injection site, on the patients who are administered anticoagulant therapy. *DEUHYO ED*, *3*, 182-186. (In Turkish).

Kuzu, N., & Ucar, N. (2001). The effect of cold on the occurrence of bruising, hematoma and pain at the injection site in subcutaneous low molecular weight heparin. *International Journal of Nursing Studies*, *38*, 51-59.

Mace, S. E. (2016). Prospective, randomized, double-blind controlled trial comparing vapocoolant spray vs placebo spray in adults undergoing venipuncture. *The American Journal of Emergency Medicine*, *34*, 798-804. doi:10.1016/j.ajem.2016.01.002

Mawhorter, S., Daugherty, L., Ford, A., Hughes, R., Metzger, D., & Easley, K. (2004). Topical vapocoolant quickly and effectively reduces vaccine-associated pain: Results of a randomized, single-blinded, placebo-controlled study. *Journal of Travel Medicine*, *11*, 267-272.

Moon, Y. E., Kim, S. H., & Choi, W. H. (2013). Comparison of the effects of vapocoolant spray and topical anesthetic cream on pain during needle electromyography in the medial gastrocnemius. *Archives of Physical Medicine and Rehabilitation*, *94*, 919-924. doi:10.1016/j.apmr.2012.12.008

Moon, Y. E., Lee, M. Y., & Kim, D. H. (2017). Preventive effect of a vapocoolant spray on propofol-induced pain: A prospective, double-blind, randomized study. *Journal of Anesthesia*, *31*, 703-708. doi:10.1007/s00540-017-2386-3

Nair, P., Kaur, S., & Sharma, Y. P. (2008). Effect of time taken in injecting subcutaneous heparin injection with reference to site pain and bruising among patients receiving heparin therapy. *Iranian Journal of Nursing and Midwifery Research*, *4*(1), 7-15.

Ogston-Tuck, S. (2014). Subcutaneous injection technique: An evidence-based approach. *Nursing Standard*, *29*, 53-58. doi:10.7748/ns.29.3.53.e9183

Olive, J. L., Hollis, B., Mattson, E., & Topp, R. (2010). Vascular conductance is reduced after menthol or cold application. *Clinical Journal of Sport Medicine*, *20*, 372-376. doi:10.1227/NEU.0b013e3181e57bca

Ozveren, H. (2011). Non-pharmacological methods at pain management. *Hacettepe University Faculty of Health Sciences Nursing Journal*, 83-92. (In Turkish). Retrived from http://dergipark.gov.tr/download/article-file/88510

Perry, A. G. (2010). Therapeutic use of heat and cold. In P. A. Potter & A. G. Perry (Eds.), *Fundamentals of nursing* (pp. 976-978). St. Louis, MI: Mosby Elsevier.

Rızalar, S., Guner, T., Kitap, T., Tes, A., Gercek, H., & Malkoc, S. (2007). The frequency of echimosis in patients with subcutaneous anticoagulan treatment. *Journal of Experimental and Clinical Medicine*, *24*, 95-99. Retrieved from http://dergipark.gov.tr/omujecm/issue/20407/215801

Shah, V., Taddio, A., McMurtry, C. M., Halperin, S. A., Noel, M., Riddell, R. P., Chambers C.T. (2015). Reducing pain during vaccine injections: clinical practice guidline. *Clinical Journal of Pain, 31*, 38-63. doi:10.1097/AJP.0000000000000281

Smeulers, M., Onderwater, A. T., van Zwieten, M. C., Vermeulen, H. (2014). Nurses' experiences and perspectives on medication safety practices: an explorative qualitative study. *Journal of Nursing Management, 22*, 276-285. doi:10.1111/jonm.12225

Testroote, M., Stigter, W. A. H., Janssen, L., & Janzing, H. M. J. (2014). Low molecular weight heparin for prevention of venous thromboembolism in patients with lower-leg immobilization. *The Cochrane Database of Systematic Reviews*, *4*, CD006681. doi:10.1002/14651858.CD006681.pub3

Varghese, C., Walia, I., Sharma, Y. P., & Kaur, S. (2006). Prevention and reduction of pain, bruise and hematoma by moist ice pack application on the site of subcutaneous heparin injection. *Nursing and Midwifery Research Journal*, *2*, 139-148. Retrieved from http://medind.nic.in/nad/t06/i4/nadt06i4p139.pdf

Yi, L. J., Shuai, T., Tian, X., Zeng, Z., Ma, L., & Song, G. M. (2016). The effect of subcutaneous injection duration on patients receiving low-molecular-weight heparin: Evidence from a systematic review. *International Journal of Nursing Sciences*, *3*, 79-88. doi:10.1016/j.ijnss.2016.02.008

Zaybak, A., & Khorshid, L. (2008). A study on the effect of the duration of subcutaneous heparin injection on bruising and pain. *Journal of Clinical Nursing*, *17*, 378-385. doi:10.1111/j.1365-2702.2006.01933.x

Zee, A. A. G., van Lieshout, K., van der Heide, M., Janssen, L., & Janzing, H. M. (2017). Low molecular weight heparin for prevention of venous thromboembolism in patients with lower-limb immobilization. *The Cochrane Database of Systematic Reviews*, *8*, CD006681. doi:10.1002/14651858.CD006681.pub4

Zeraatkari, K., Karimi, M., Shahrzad, M. K., & Changiz, T. (2005). Comparison of heparin subcutaneous injection in thigh, arm and abdomen. *Canadian Journal of Anesthesia*, *52*, 109. doi:10.1007/BF03023147

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