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ORIGINAL ARTICLE

Effectiveness of skin icing in reducing pain associated with goserelin acetate injection

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Abstract
Background Goserelin acetate, which is injected through a 16-gauge needle, makes some patients feel substantial, although tolerable, pain. We tried to clarify whether injection pain was reduced by icing the skin at the injection site.
Methods Pain associated with the injection of goserelin acetate was prospectively evaluated in 48 patients who had received an 10.8-mg goserelin injection at least once previously. In this study, the first injection was administered by usual methods, and 3 months later a second injection was administered after icing the skin at the injection site. Pain intensity was evaluated by visual analogue scale (VAS) pain score.
Results VAS pain scores for the usual injection method were 32.4 ± 21.7 mm [mean $\pm$ 2 standard deviation (SD)] and was significantly lower (16.4 ± 17.9) for the icing method ($p = 0.001$, paired t test). Thirty-three (68.8%), eight (16.7%), and seven (14.6%) of the 48 patients reported a decrease, no change, and increase, respectively, in VAS pain score by the icing method.
Conclusions Icing at the injection site of goserelin acetate is a safe and effective method to reduce injection pain. This method can be easily performed in daily practice if a patient complains of pain at the injection site.

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Introduction

Luteinizing-hormone-releasing hormone (LH–RH) analogues, such as goserelin acetate (Zoladex, AstraZeneca) and leuprorelin acetate (Leuprin, Takeda) are mainstays of endocrine therapy used for treating advanced prostate cancer. These medicines are administrated by subcutaneous injection every 3 months. Pain associated with the injection is tolerable for almost all patients. However, some patients complain of pain at the injection site. Goserelin acetate consists of a solid depot and is injected through a 16-gauge needle. This needle, along with real pain, generally instills in patients a fear of the image of a larger needle, which could influence pain intensity. Conflicting results have been reported regarding pain associated with goserelin acetate injection. A randomized crossover study demonstrated that patients preferred injection of leuprorelin acetate via a smaller needle than goserelin acetate using a larger needle [1]. However, in contrast, another study showed that if injection was performed with the patient blinded, injection pain intensity was not significantly different between leuprorelin acetate administration with a small needle and goserelin acetate administration using a larger needle [2]. Even if injection pain is tolerable, it is important for patients to have minimum injection pain associated with goserelin acetate. The effectiveness of icing or cooling the skin has been reported to reduce sensation and is applied in various medical fields. In this study, we investigated whether icing at the injection site of goserelin acetate is an effective method to reduce injection pain.

Patients and methods

From April 2006 to March 2007, 48 consecutive patients who gave informed consent participated in this prospective study. Patients were diagnosed with prostate cancer and had received subcutaneous injection of goserelin acetate (10.8 mg) at least once before participating in this study. Patient demographic variables are demonstrated in Table 1. The median age was 73 (range 55–90) years, and the median number of goserelin injections received before this study was four (range 1–35). Pain associated with the injection was evaluated by visual analogue scale (VAS) pain score, which was described from 0 mm (no pain) to 100 mm (maximum pain expected). First, patients received an injection of goserelin acetate (usual method). In our department, the injection was performed in the lower abdomen by nurses who were trained to administer this injection. The nurse inserted two thirds of the needle into the subcutaneous tissue. Needle direction was approximately 30° caudal from the perpendicular direction. Three months later, the patients received a goserelin acetate injection after self-application of a refrigerant at the injection site for approximately 30 s (icing method). The refrigerant had been stored at −10°C. Before the patient used the refrigerant, it was placed in warm water until its surface melted. The patients wrapped the refrigerant with gauze and applied it to the injection site. VAS pain scores between the two methods were compared. Statistical analyses were performed with a paired *t* test and chi-square test. A p value <0.05 was considered statistically significant.

Table 1 Patient characteristics

Demographics	Statistics
Median age	73 (55–90)
Median PSA (ng/ml)	34 (1.0–2000)
Stage	
B	20
C	13
D	15
Gleason score	
≤6	21
7	10
≥8	13
Unknown	4
Median no. of injections before this study	4 (1–35)
Age and VAS pain score (mean)	
<73 years old	32.6
≥73 years old	32.3
No. of injections before this study and VAS pain score (mean)	
≤3 times	31.8
≥4 times	33.4

PSA prostate-specific antigen, *VAS* visual analogue scale pain score

Results

Mean VAS pain score of the icing method was significantly lower [16.4 ± 17.9 mm; mean ± 2 standard deviation (SD)] than that of the usual injection method (32.4 ± 21.7 mm); $p = 0.001$, paired *t* test) (Fig. 1). Eight patients (16.7%) indicated a VAS pain score <13 mm with the usual method and 25 (52.0%) with the icing method. Figure 2 shows the waterfall graph representing the difference of VAS pain score between the two injection methods. The number of patients with a decrease, no change, or an increase in VAS pain score after changing to the icing method was 33 (68.8%), eight (16.7%), and seven (14.6%), respectively. When patients were divided into two subgroups according to VAS pain score of the usual injection, group 1 (patients with a VAS ≤32 mm, $n = 26$) and group 2 (patients with a VAS >33 mm, $n = 22$), 15 patients (57.7%) in group 1 and 18 patients (81.8%) in group 2 demonstrated a reduction in pain associated with the icing method (Fig. 3) ($p = 0.072$, Chi-square test).

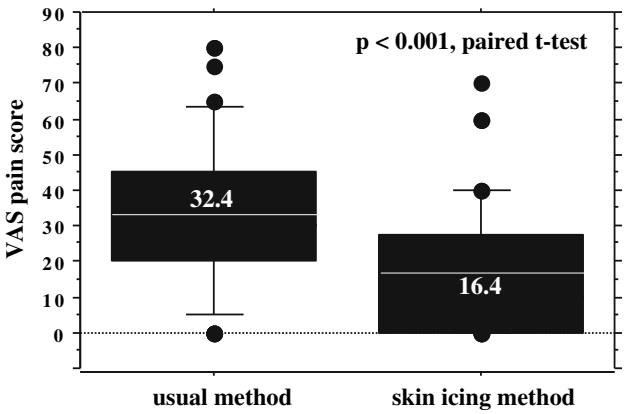

Fig. 1 Significant reduction in injection pain after skin icing

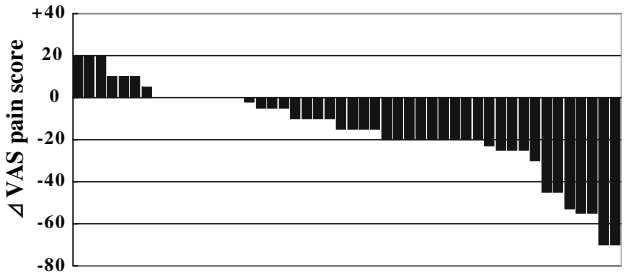

Fig. 2 Waterfall graph representing changes in injection pain after skin icing

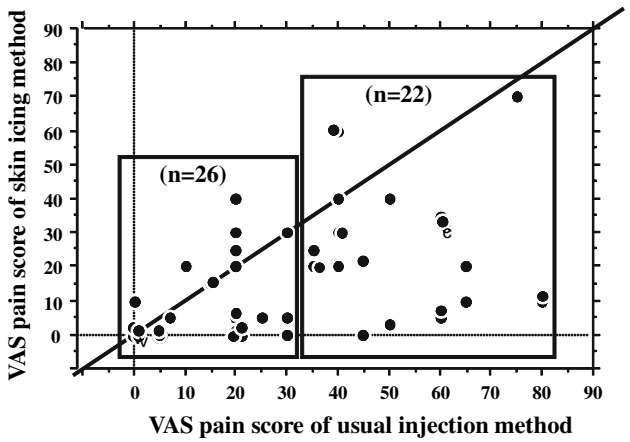

Fig. 3 Changes in injection pain according to basal visual analogue scale (VAS) pain score for each patient

Age and number of injections before the study did not influence the VAS pain score of the usual method. The mean VAS pain scores for the subgroup of patients aged ≤73 years and for patients aged >73 years were 32.6 mm ($n = 23$) and 32.3 mm ($n = 25$), respectively. The mean VAS pain scores for the subgroups of patients who had at least three or fewer injections before this study and those with more than three injections were 31.8 mm ($n = 23$) versus 33.1 mm ($n = 25$), respectively.

Discussion

Only a few studies have evaluated injection pain of LH–RH analogues. Williams et al. demonstrated that the tolerability of leuprorelin acetate was better than that of goserelin acetate by a randomized crossover trial. The use of a 16-gauge needle for goserelin acetate rather than a 23-gauge needle of leuprorelin acetate may influence their results [1]. On the other hand, Montgomery et al. [2] demonstrated that there was no significant difference in pain intensity between goserelin acetate and leuprorelin acetate when patients received them in a blinded manner. It is important to note that the majority of patients who participated in these two studies reported a VAS pain score <13 mm, which may be considered clinically insignificant [3, 4]. However, in our study, the mean VAS pain score with the usual method (32.4 mm) was higher than that of previous reports, and just 16.7% of patients reported a VAS pain score <13 mm. These results may be explained by the differences in body mass index, race, culture, and expectation for the medical treatment between Caucasian and Japanese patients. In our study, patient age and number of previous goserelin acetate injections did not influence VAS pain score of the usual injection method. These results suggest that patients may not get used to the pain of goserelin acetate injection, even if they have received it for a long time.

The use of skin cooling or icing to reduce pain has been applied in various medical procedures, such as laser therapies, minor surgical procedures, and plastic surgeries. Bechara et al. [5] demonstrated that icing the injection site of botulinum toxin for hyperhidrosis clearly decreased pain intensity. Furthermore, another randomized study proved that pretreatment cooling with frozen gel packs applied in the axilla could reduce pain of axillary injections of botulinum toxin [6]. In our study, we also showed that application of a refrigerant to the injection site caused significant reduction in injection pain. After icing, the mean VAS pain score decreased from 32.4 to 16.4 mm. This difference of 13 mm and greater was considered clinically significant according to previous studies [3, 4]. After application of a refrigerant to the injection site, the VAS pain score decreased in 68.8% (33 of 48) of patients. Even if the difference of the VAS pain score <13 mm was considered insignificant, 52.0% (25 of 48) of patients experienced slight pain. When the patients were divided into two subgroups according to VAS pain scores with the usual injection method, skin icing was more effective in reducing injection pain in patients with higher scores.

Our study has some limitations. The degree of pain experienced by the patients after injection was influenced by various factors, although the injection was performed in the conventional manner. VAS pain score was measured only once during each procedure. In order to eliminate the influence of various factors, the VAS pain score should be repeatedly measured to obtain more reproducible and conclusive results. For example, seven patients who used the icing method showed a high VAS pain score. This increase in pain may be attributed to accidental injury of free nerve endings by the needle or induced by the icing procedure itself or the limitations in the pain-monitoring method. Moreover, there was a possible bias in that patients expected less pain when ice was applied, because people are aware of the effectiveness of icing or cooling at the painful site. This expectation may also influence the results of our study. This bias is, however, difficult to eliminate, even in well-designed clinical studies, because patients notice icing and may expect something to occur in the injection site, even if they were blinded. Pain intensity, even in the same situation, may be influenced by various conditions. Thus, expectancy of less pain after icing could be an important indirect parameter that accounts for reducing real pain. Another possible bias may be the order of the injection method, the first usual and the second icing. However our data showed that the number of goserelin acetate injections prior to the study did not influence VAS pain score (Table 1). Therefore, this bias may be considered minimal.

In conclusion, we demonstrated that more than half of the Japanese patients felt less pain at the goserelin acetate injection site after icing. Several medical workers may consider that the pain associated with injection is minimal and can, thus, be ignored. However, a substantial number of elderly men feel considerable pain, although tolerable. Icing the skin at the injection site is easy, inexpensive, and safe. If this simple method is likely to be beneficial for some patients, physicians should try this in order to reduce their patients' pain.

Conflict of interest statement None.

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