Characteristics of Pain Following Intracavernous Injection of Prostaglandin E1

The aim of this study was to determine the incidence and characteristics of pain following intracavernous injection of prostaglandin E1(PGE). We injected PGE into the cavernous tissues of 156 patients with erectile dysfunction who had never previously been injected with PGE. The incidence and characteristics of pain after injection were evaluated by the patients' response to a questionnaire. The intensity of pain was determined by the degree of impediment to intercourse, verbal rating scale (VRS), numerical rating scale (NRS), and visual analogue scale (VAS). Patients scoring 'no pain' on the VRS, NRS, and VAS were 11.5%, 7.7%, and 7.7%, respectively. Overall incidence of pain was 91%. There was 'much' or 'very much' impediment to intercourse because of pain in 14 (9.1%) patients. The most common kind of pain was 'heavy pain' in 90% of the patients followed by 'throbbing' in 38%, 'aching' in 21%, 'tightening' in 18%, and 'shooting' in 13%. The mean duration of pain was 101.2±63.7 minutes and it lasted during the entire erection period in 71(50.4%) patients. There were significant correlations among the degree of impediment to intercourse, VRS, NRS, and VAS scores (all $p<0.01$). However, no association was noted between pain intensity and both erectile response to PGE and injected dose. The higher incidence of intracavernous PGE-induced pain reported here compared to other studies might be related to difference in pain thresholds among races. The high incidence of pain but low frequency of much impediment to intercourse would be related to the pain characteristics as well as the intensity of pain. *(JKMS 1997; 12: 327~31)*

Key Words : *Erectile dysfunction, Prostaglandin E1, Intracavernous injection, Pain*

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INTRODUCTION

Prostaglandin E1 (PGE) is widely used for intracavernous injection therapy due to its efficacy of producing erections and low rate of complications such as prolonged erection and fibrous plaque formation, as compared to other vasoactive agents (1, 2). The principal deterrent to PGE use in intracavernous injection is that it causes pain in 11.5 to 80% of the patients (3~5). At the present, no definitive explanation for the variable rates of pain reported in intracavernous PGE studies exists. A variety of factors, including formulation differences (3), administration methods (6), dosages (7), and underlying diseases (8) may account for the variable reported pain rates. The kinds and duration of pain during intracavernous PGE-induced erection have been inadequately studied.

Verbal rating scales (VRS), numerical rating scales (NRS), and visual analogue scales (VAS) have been widely used for the measurement of pain. These tools provide a high degree of sensitivity, reproducibility, and test-retest reliability (9~11). Measurement of the degree of impediment to intercourse has been a frequently used method for evaluating pain associated with intracavernous injection of PGE (3, 12~14). However, the correlation between this method and VRS, NRS, and VAS has been inadequately investigated.

The aims of this prospective study were : 1) to assess the incidence and characteristics of pain following intracavernous injection of PGE, 2) to determine the correlations among the degree of impediment to intercourse, VRS, NRS, and VAS in the evaluation of pain intensity, and 3) to assess the relationships between pain intensity and history of diabetes mellitus, and between pain intensity and both dose and erectile response to PGE.

MATERIALS AND METHODS

The initial evaluation for patients presenting to our sexual dysfunction clinic with erectile dysfunction in-

cluded medical and sexual history, physical examination, and laboratory tests. Following this evaluation, PGE (Alprostadil sterile powder or Caverject, Pharmacia and Upjohn Inc., MI) was injected intracavernously to determine the optimal dose when patients wanted intracavernous pharmacotherapy. A total of 156 patients 24 to 77 years (mean age 52.6±10.9) who had never previously been injected with PGE were enrolled in this study. The patients were injected with 10 μg to 20 μg PGE (10 μg in 17, 15 μg in 19, 20 μg in 120) according to the etiology of erectile dysfunction, age of patients, and their penile size by the same investigator using 29 gauge needles. Speed of injection and administration of medication was similar in all patients. The erectile response was determined by inspection and palpation of the penis by the same investigator, and described as poor (absent or insufficiently rigid erection for vaginal intromission), moderate (partially rigid erection probably sufficient for vaginal intromission) or good (an erection with adequate attainment and duration of rigidity for satisfactory intercourse).

Following intracavernous injection of PGE, the patients completed a questionnaire which had a 6-item scale that assessed kinds, duration, and intensity (degree of impediment to intercourse because of pain, VRS, NRS, and VAS) of the pain experienced during erection and thereafter. The patients read the 12 kinds of pain descriptors which were contained in our modification of the short-form McGill Pain Questionnaire (15), and chose the words that best described their pain. The VRS used a four-word scale : 'No, Mild, Distressing, Horrible'. The NRS used an 11-point scale where 0='no pain' and 10 ='most excruciating pain imaginable'. The VAS used a 10 cm line with 0 at one end and 10 ('worst pain') at the other. The degree of impediment to intercourse because of pain was described as none, slight, moderate (intercourse still possible), much (intercourse unlikely), and very much (intercourse impossible). We regarded 'much' or 'very much' responses as indicators of impediment to intercourse. We regarded presence of pain as experience of any pain regardless of its severity, and calculated the overall incidence of pain by comprehensive analysis of patients' reports on VRS, NRS, VAS, and the degree of impediment to intercourse. If pain had not disappeared within 1 hour after the injection, we advised the patients to return home and inform the duration of pain by telephone.

Pearsons correlation analysis was used to assess correlations among the pain scores of VRS, NRS, VAS and the degree of impediment to intercourse. Students's t test and one-way analysis of variance (ANOVA) test were used for the comparison of the NRS and VAS scores with erectile responses to PGE, doses of PGE administered, and history of diabetes mellitus. Results were considered statistically significant when $p<0.05$.

RESULTS

Patients scoring 'no pain' and 'distressing or horrible pain' on the VRS were 18 (11.5%) and 13 (8.4%), respectively (Table 1). The mean plus or minus standard deviation of the NRS and VAS scores were 3.38±1.91 and 3.3±2.05, respectively. Patients scoring '0' point on the NRS and VAS were 12 (7.7%) and 12 (7.7%), respectively (Table 2). There was 'much' or 'very much' impediment to intercourse because of pain in 14 (9.1%) of the 156 patients (Table 3). A total of 12 patients reported 'no pain' on all the evaluation methods for pain. In 2 patients, there was pain of 1 point on both NRS and VAS but no pain on other assessment methods (VRS and impediment to intercourse), and we included these subjects among patients without pain. Of the 18 patients who answered 'no pain' on the VRS, 4 reported pain

Table 1. Pain intensity on the verbal rating scale (VRS) following intracavernous injection of PGE

VRS	No. of patients (%)
No	18 (11.5)
Mild	125 (80.1)
Distressing	11 (7.1)
Horrible	2 (1.3)
Total	156

Table 2. Pain intensity on the numerical rating scale (NRS) and visual analogue scale (VAS) following intracavernous injection of PGE

Point \ Intensity	NRS No. of patients (%)	VAS No. of patients (%)
0	12 (7.7)	12 (7.7)
1 - 3	86 (55.1)	89 (57.1)
4 - 6	47 (30.1)	42 (26.9)
7 - 10	11 (7.1)	13 (8.3)
Total	156	156

Table 3. The degree of impediment to intercourse because of pain following intracavernous injection of PGE

Degree	No. of patients (%)
None*	61 (39.1)
Slight	34 (21.8)
Quite	47 (30.1)
Much	13 (8.3)
Very much	1 (0.7)
Total	156

* No pain or no impediment

Table 4. Kinds of pain following intracavernous injection of PGE

Kinds	No. of patients (%)
Heavy	127 (90.0)
Throbbing	54 (38.3)
Aching	29 (20.6)
Tightening	26 (18.4)
Shooting	18 (12.8)
Others	56 (39.7)
Total	141

Table 5. Duration of pain following intracavernous injection of PGE

Duration	No. of patients (%)
Disappeared a few minutes later	8 (5.7)
During the rigid phase	38 (27.0)
During the entire erection period	71 (50.4)
Persistent after loss of erection	24 (17.0)
Total	141

Mean duration: 101.2±63.7 minutes

Table 6. Correlation coefficients among the degree of impediment to intercourse, verbal rating scale, numerical rating scale and visual analogue scale for measurement of pain

	Impediment	VRS	NRS	VAS
Impediment	X	0.51	0.56	0.56
VRS	0.51	X	0.69	0.64
NRS	0.56	0.69	X	0.91
VAS	0.56	0.64	0.90	X

* All p Value < 0.01(Pearson's correlation analysis was used to assess correlations among the pain scores of VRS, NRS, VAS, and the degree of impediment to intercourse

Table 7. The numerical rating scale and visual analogue scale scores according to dose, erectile response to PGE, and history of diabetes mellitus

Variables (No. Pts.)	NRS	VAS
Dose		
10 μg (17)	4.47±2.27	4.35±2.40
15 μg (20)	3.84±2.44	4.00±2.40
20 μg (119)	3.15±1.71*	3.03±1.88*
Erectile response		
Poor, Moderate (62)	3.35±2.14	3.22±2.20
Good (94)	3.39±1.76	3.34±1.97
	(p=0.91)	(p=0.73)
DM**		
Presence (27)	3.66±1.82	3.56±2.10
Absence (129)	3.31±1.93	3.24±2.05
	(p=0.76)	(p=0.82)

All results are expressed as mean ±S.D.
* Significantly different from 10 μg (p= 0.013).
** Diabetes mellitus

on the other tests and were included among patients with pain. Therefore, overall incidence of pain with PGE was calculated as 91.0% (142/156).

The most common kind of pain was 'heavy pain' in 90% of the patients, followed by 'throbbing' in 38.3%, 'aching' in 20.6%, 'tightening' in 18.4%, 'shooting' in 12.8% and others in 39.7% ('tender' in 9.2%, 'sharp' in 7.1%, 'stabbing' in 6.4%, 'burning' in 5.0%, 'splitting' in 5.0%, 'cramping' in 3.5%, and 'gnawing' in 3.5%) (Table 4). The mean duration of pain was 101.2± 63.7 minutes, with a range from 2 to 300 minutes, and it lasted during the rigid phase of erection in 38 (27.0%), during the entire erection period in 71 (50.4%), and persisted after loss of erection in 24 (17.0%) (Table 5).

There were significant correlations among the degree of impediment to intercourse, VRS, NRS and VAS scores (all $p<0.01$) (Table 6). There was no significant difference in VRS and NRS scores between the patients with and without diabetes mellitus (Table 7). Also, no association was noted between pain intensity and both injected dose and erectile response to PGE (Table 7).

DISCUSSION

The usefulness of intracavernous injection of PGE for the diagnosis and treatment of erectile dysfunction has been established. When doses in the range of 10~20 micrograms are injected, erections sufficiently rigid to allow successful intercourse result in 61~79% of patients with erectile dysfunction of varying etiologies (1). The principal drawback to self-injection therapy with PGE for erectile dysfunction is penile pain. Such pain may be localized to the injection site, or more commonly, may occur along the entire penile shaft during erection (4). Understandably, this painful side-effect is a common reason for patients discontinuing self-injection therapy using this agent (16).

In our study, the incidence of penile pain during intracavernous PGE-induced erection was as high as 91% despite using a new formulation (Caverject). In other investigations using the same formulation of PGE, penile pain after injection occurred in 15.9 to 20% of the patients during the dose-finding phase (4, 13). There are several possible explanations for this disparity between our results and those in published reports, in addition to differences in dose and administration technique. A possible reason is that pain thresholds may vary among individuals or races. A second possible explanation may be in the criteria and assessment tools for pain. It is difficult to establish the criteria for whether pain exists or not because only the patients themselves can feel their pain and they express its intensity in different ways. For

example, patients' pain scores were underestimated by healthcare providers, such as physicians, nurses, and house officers, and not correlated with those of clinical staff for the patients with severe pain in a study of cancer pain (17). We regarded presence of pain as the experience of any pain regardless of its severity, and then calculated the overall incidence of pain by comprehensive analysis of patients' pain with questionnaires which were filled out by themselves.

In other series, common kinds of pain after injection of PGE were aching and burning sensations (12, 16, 18). However, in this study the most common complaint was 'heavy' pain followed by 'throbbing', 'aching' and 'tightening' sensations lasting during the entire erection period. The higher incidence of pain in our study compared to other reports but low frequency of much impediment to intercourse would be partly related to the pain characteristics. The mean duration of pain was longer in our patients than that of Godschalk et al. (19). In addition, this pain persisted after loss of erection (17%) as well as during the entire (50%) or rigid erection periods (27%).

Although VRS, NRS, and VAS are based upon single patient's self-reporting, these tools are easy for the patients to use and understand. Since both the NRS and VAS provide a high validity and reliability, and can be assessed parametrically, these tools have been frequently used as outcome measurements in clinical trials (20). Measurement of the degree of impediment to intercourse has been used to assess pain with intracavernous injection of PGE, but the reliability of this method has been ill-defined (3, 12~14). We found that the degree of impediment to intercourse was well correlated with the scores on VRS, NRS, and VAS. Also, there were significant correlations among the VRS, NRS, and VAS scores. Therefore, measurement of the degree of impediment to intercourse may be a useful and simple method of evaluating the pain associated with PGE. In addition, both the VAS and NRS might be rapid, reliable, and valid tools for outcome measurements in clinical trials that investigate reduction of the pain associated with injection of PGE.

The etiology of pain following injection with PGE is not well understood. Several investigators have reported that the dose of PGE administered may be associated with the pain from intracavernous injection (5, 7, 21). However, Gerber and Levine (16) reported no dose-related increase in severity or duration of post-injection pain. Nor was a relationship between the incidence of pain and injected dose reported by Chen et al. (4). Although our non-randomized, open-labeled study had a disproportionately large number of subjects at 20 μg compared to those at 10 μg and 15 μg, we found no differences in pain intensity among these doses. Schramek et al. (22) hypothesized that the possible cause of the pain is pharmacologically-induced vasodilation. We, therefore, evaluated differences of pain intensity according to erectile response to PGE. There was no significant difference in pain intensity between the patients who showed good erectile response to PGE and those who did not. This result suggests that pain is unlikely to be associated with PGE-induced vasodilation. Linet et al. (23) reported that the incidence of pain with PGE was significantly higher in impotent patients with diabetes mellitus (65%) than in non-diabetic patients (48%). In our study, no difference in pain intensity was noted between diabetic and non-diabetic patients.

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