Original Article

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Comparison of efficacy and safety in the combination therapies of duloxetine and S-flurbiprofen plaster, and of duloxetine and conventional NSAIDs for chronic pain in patients with osteoarthritis (OASIS DUAL study)

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SUMMARY The purpose of this study is to compare the efficacy and safety of pharmacotherapies for chronic pain due to osteoarthritis (OA) between a group with duloxetine (DLX) and S-flurbiprofen plaster (SFPP) (the SFPP group) and a group with DLX and conventional non-steroidal anti-inflammatory drugs (NSAIDs) (the control group). The subjects were 49 patients (17 men and 32 women). The evaluation of factors associated with treatment termination due to symptoms improvement showed that significantly more women terminated treatment than did men, and significantly more members of the SFPP group terminated treatment than did members of the control group. The visual analogue scale (VAS) score in the SFPP group was significantly improved from 6.6 ± 1.7 before treatment to 3.6 ± 2.1 one month later and showed significant difference until nine months later. The VAS score in the control group was significantly improved from 6.7 ± 1.9 to 4.1 ± 2.8 one month later. The VAS score improvement rate was significantly higher in the SFPP group than in the control group, suggesting that the DLX-SFPP combination had higher efficacy than the DLX-conventional NSAIDs combination. The incidence of adverse drug reactions was 55% in the SFPP group, which is not significantly different from 50% incidence in the control group. The treatment discontinuation rate due to adverse drug reactions, however, was 60% in the control group and 19% in the SFPP group. It was suggested that the efficacy and safety of the DLX-SFPP combination for chronic pain due to OA are equal to or higher than that of the DLX-conventional NSAIDs combination.

Keywords Chronic pain, osteoarthritis, pharmacotherapy, duloxetine, S-flurbiprofen plaster

1. Introduction

Osteoarthritis (OA) is a disease that causes osteoplastic change in joints in a non-inflammatory and progressive manner and adds inconveniences to the activities of daily living (ADL) because of pain (*1*). OA prevalence increases with age. According to the large-scale population-based cohort study, the number of patients (40 years of age or older) who have OA of the knee is estimated to be 25.3 million, that of patients who have lumbar spondylosis 37.9 million, and that of patients who have OA of the hip 12.0 million in Japan (*2*). Since OA progresses chronically, it often causes chronic pain. It influences various ADL, reduces healthy life expectancy (*3*), and raises mortality (*4,5*). Therefore, OA is a considerable social problem.

The pathology of chronic pain from OA is complex because acute pain is often involved in the course of chronic pain. It makes treatment difficult (*6*). It is expected that appropriate treatment of chronic pain not only extends healthy life expectancy, but also reduces healthcare costs and premiums for nursing-care insurance. Clinical Practice Guidelines for the Management of Chronic Pain strongly recommend duloxetine (DLX) for OA (*7*), but oral non-steroidal anti-inflammatory drugs (NSAIDs) are often used chronically. The use of oral long-term NSAIDs causes adverse drug reactions, including gastric mucosa injury (*8*), cardiovascular risk (*9*), and renal dysfunction (*10*). There is also a problem of polypharmacy in the elderly. Therefore, it is necessary to consider the details of drug prescriptions.

Topical NSAIDs are the most strongly recommended according to the latest guidelines by the Osteoarthritis Research Society International (OARSI), and oral NSAIDs are conditionally recommended (*11*). Among

topical NSAIDs, S-flurbiprofen plaster (SFPP) has a stronger analgesic effect than topical flurbiprofen (*12*). The efficacy of long-term SFPP administration has been reported (*13*), and the incidence of serious adverse drug reactions in the digestive system was relatively low (*14*). As a drug used in combination with DLX for chronic pain due to OA, SFPP is expected to be effective. There are, however, few reports of combination therapy with DLX and no data comparing DLX with conventional NSAIDs and DLX with SFPP. If the DLX-SFPP combination shows efficacy equal to that of the DLX-conventional NSAIDs combination, and if safety is confirmed and adverse drug reactions and polypharmacy are taken into account, treatment with DLX and SFPP can be a useful option.

The purpose of the present study is to compare the efficacy and safety of pharmacotherapies for chronic pain due to OA between the SFPP group and the control group.

2. Materials and Methods

2.1. Ethical approval of the study protocol

The present study was approved by the clinical research ethical review board of Shido, Inc. (#S20220131) and conducted in accordance with the Declaration of Helsinki and the ethical guidelines provided by the Ministry of Health, Labour and Welfare. Since my clinic does not have an ethics review committee, I asked an external committee to review this study. As it did not involve invasive procedures for the patients or other intervention and used only medical information, an opt-out was provided to patients for the disclosure of information.

2.2. Study design and subjects

The study was designed as a single-center, retrospective study in Japan. I included only the existing data in the analysis; no new data were collected. The subjects were 49 patients who received pharmacotherapy for chronic pain due to OA in my hospital from January 2018 to October 2021 and used oral DLX and oral or topical NSAIDs and whose visual analogue scale (VAS) scores were measured. Lumbar spondylosis was not included, since lower back pain is not caused by lumbar spondylosis alone, but is also often caused by more than one disease. There were 17 men and 32 women, and their mean age was 71.8 ± 10.2 years.

2.3. Investigation items

I speculated that improving chronic pain due to OA and terminating treatment early are important to improve the quality of life (QOL) of patients. Therefore, as part of the primary endpoint analysis, I evaluated sex, age, the presence or absence of SFPP treatment, and VAS score as factors associated with the termination of treatment due to the improvement of symptoms. Secondary endpoints were time to the termination of treatment due to the improvement of symptoms; changes in VAS score 1, 3, 6, 9, 12, 18, and 24 months from the start of administration; VAS score improvement rates before and after the start of treatment; the incidence of adverse drug reactions; and the treatment discontinuation rate due to adverse drug reactions.

2.4. Statistical analysis

The primary endpoint was an event of treatment termination due to the improvement of symptoms, and the time from treatment initiation to the occurrence of an event or censoring was evaluated using a Cox proportional hazards model with age, sex, the presence or absence of SFPP treatment, and VAS score as covariates. Regarding secondary endpoints, Kaplan-Meier curves of time from the start of treatment to the end of treatment in the SFPP group and the control group were drawn and tested using the log-rank test. Regarding changes in VAS score 1, 3, 6, 9, 12, 18, and 24 months from the start of treatment, intragroup comparison in the SFPP group and in the control group was tested using the Wilcoxon signed rank test and intergroup comparison was tested using the Wilcoxon rank sum test. Regarding the amount of change in the VAS score from the start of treatment to the end of treatment due to the improvement of symptoms, intragroup comparison in the SFPP group and in the control group was tested using the Wilcoxon signed rank test. Regarding the VAS score improvement rate, treatment outcomes were classified in order to investigate efficacy as follows: improved (improvement rate ≥ 50%), somewhat improved (improvement rate > 0% to < 50%), unchanged (improvement rate 0%), somewhat worsened (improvement rate < 0% to > −50%), and worsened (improvement rate ≤ – 50%). According to the formula of Hirabayashi (*14*), the VAS score improvement rate was defined as (VAS score before treatment – VAS score after treatment) × 100 / (10 – VAS score before treatment). The VAS score improvement rate, the incidence of adverse drug reactions, and the treatment discontinuation rate due to adverse drug reactions between the SFPP group and the control group were tested using Fisher's exact test. Regarding backgrounds of the subjects, variables on a nominal scale were compared using Fisher's exact test, and continuous variables were compared using Student's *t*-test. R version 3.5.2 (R Foundation for Statistical Computing, Vienna, Austria [*https://www.R-project.org/*]) was used for analysis.

3. Results

In the present study, the SFPP group had 29 patients (12

men and 17 women) with a mean age of 71.7 ± 10.1 years. The control group had 20 patients (5 men and 15 women) with a mean age of 72.1 ± 10.8 years. No significant difference was observed in men-to-women ratio or age between the two groups. A breakdown of primary diseases and previous histories of hypertension, hyperlipidemia, diabetes mellitus, and gout in both groups are shown in Table 1.

The VAS score before the start of treatment was 6.6 ± 1.7 in the SFPP group and 6.7 ± 1.9 in the control group, showing no significant difference. Regarding oral doses of DLX, the starting dose was 20 mg in both groups, the mean maximum dose was 43.3 ± 13.9 mg in the SFPP group and 40.0 ± 16.6 mg in the control group, and the mean maintenance dose was 38.6 ± 14.4 mg in the SFPP group and 38.9 ± 17.2 mg in the control group, showing no significant difference. In the SFPP group, all patients used SFPP concurrently, and the maximum dose was two plasters a day irrespective of application sites. In the control group, 14 patients used oral NSAIDs (celecoxib in eight patients, loxoprofen sodium in four patients, and diclofenac sodium in two patients) concurrently, and 20 patients used a topical NSAID (loxoprofen sodium hydrate patch in all patients) concurrently. The maximum doses of the oral NSAIDs were as follows: celecoxib 200 mg/day, loxoprofen sodium 180 mg/day, and diclofenac sodium 75 mg/day. The maximum dose of the topical NSAID, loxoprofen sodium hydrate patch, was one patch daily. The mean duration of drug administration was eight months in the SFPP group and ten months in the control group. Regarding concurrently used antiemetics, mosapride was significantly more common in the SFPP group (28 patients in the SFPP group and 12 patients in the control group) and metoclopramide was significantly more common in the control group (one patient in the SFPP group and eight patients in the control group).

Table 1. Primary diseases and previous histories in two groups

Items	SFPP group (n = 29)	Control group (n = 20)	p
Primary disease			0.865
Osteoarthritis of the cervical spine	1 (3.4%)	0 (0%)	
Osteoarthritis of the shoulder	2 (6.9%)	1 (5.0%)	
Osteoarthritis of the wrist	1 (3.4%)	0 (0%)	
Osteoarthritis of the hip	4 (13.8%)	5 (25.0%)	
Osteoarthritis of the ankle	4 (13.8%)	4 (20.0%)	
Osteoarthritis of the knee	17 (58.6%)	10 (50.0%)	
Previous history			
Diabetes mellitus	5 (17.2%)	1 (5.0%)	0.379
Hypertension	16 (55.2%)	13 (65.0%)	0.563
Hyperlipidemia	7 (24.1%)	6 (30.0%)	0.747
Gout	2 (6.9%)	3 (15.0%)	0.387

Data are n (%). N.S., Fisher's exact test. SFPP: S-flurbiprofen plaster.

Table 2. Multivariate analysis using a Cox proportional hazards model with discontinuation due to the improvement of symptoms as an event (n = 49)

Items	Hazard ratio	95% CI	p
Age	1.011	0.966 - 1.059	0.631
Sex (man:1, woman:0)	0.254	0.071 - 0.913	0.036*
Group (SFPP group:1, control group: 0)	4.034	1.156 - 14.076	0.029*
VAS	0.932	0.702 - 1.237	0.626

*p < 0.05, Multivariate analysis using a Cox proportional hazards model. SFPP: S-flurbiprofen plaster; VAS: visual analog scale.

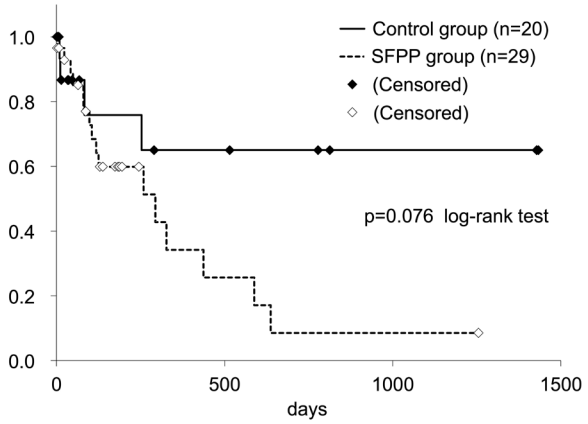

Figure 1. Kaplan-Meier curves with discontinuation due to the improvement of symptoms as an event.

3.1. Primary endpoint

The results of the evaluation of factors associated with the termination of treatment due to the improvement of symptoms showed that the termination of treatment was significantly more likely in women and the SFPP group (Table 2).

3.2. Secondary endpoints

Time to the termination of treatment due to the improvement of symptoms tended to be shorter in the SFPP group, but the difference between the two groups was not significant (Figure 1).

The mean VAS score in the SFPP group was significantly improved from 6.6 ± 1.7 before treatment to 3.6 ± 2.1 one month later and showed significant difference until nine months later (Figure 2a). Regarding the VAS score improvement rate in the SFPP group, scores were improved and somewhat improved in 86.2% of the patients and worsened and unchanged in 13.8%.

The mean VAS score in the control group was significantly improved from 6.7 ± 1.9 before treatment to 4.1 ± 2.8 one month later, but did not show significant difference after that (Figure 2b). Regarding the VAS score improvement rate in the control group, scores were improved and somewhat improved in 60%

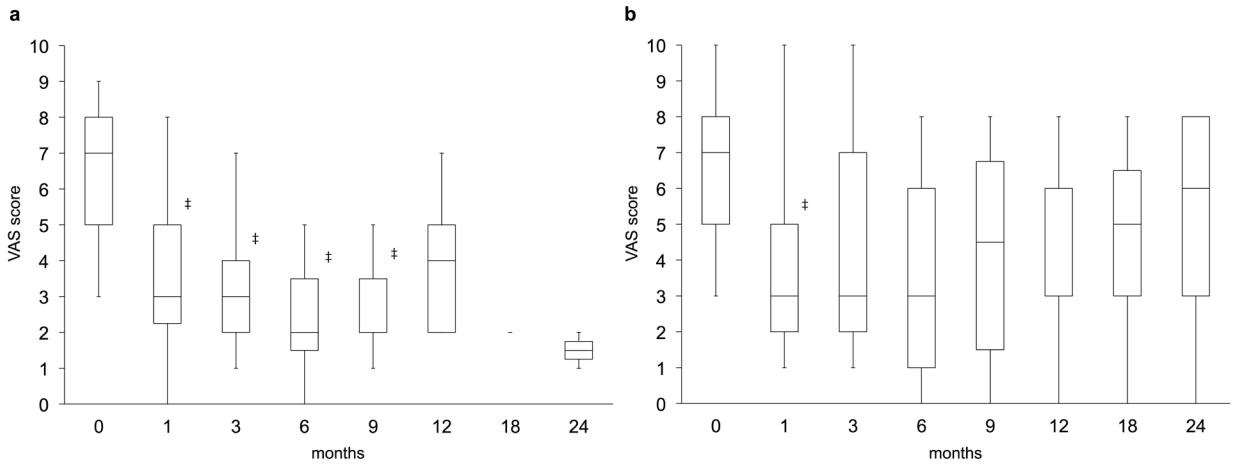

Figure 2. Change in VAS score. a: SFPP group. b: Control group. ‡$p < 0.05$ *vs.* 0 M. Wilcoxon signed rank test. Data are min-1stQ-median-3rdQ-max.

of the patients and worsened and unchanged in 40%.

When VAS scores were compared between the two groups, there was no significant difference during the follow-up period, including the observation period before treatment. Regarding the VAS score improvement rate, the proportion of patients who had improved and somewhat improved scores was significantly higher in the SFPP group, and the proportion of patients who had worsened and unchanged scores was significantly higher in the control group (Figure 3).

The incidence of adverse drug reactions in the SFPP group was 55% (16/29 patients), and the breakdown of the adverse drug reactions was as follows: nausea in seven patients, sleepiness in six patients, gastrointestinal disorder in five patients, constipation in one patient, thirst in one patient, and skin disorder in one patient. The rate of treatment continuation (defined as "treatment continuation or treatment termination due to improvement," and treatment termination due to any other reason was regarded as "treatment discontinuation") was 76%, and reasons for discontinuation were adverse drug reactions in three patients, worsening in one patient, and unknown in three patients. The treatment discontinuation rate among patients who developed adverse drug reactions was 19% (3/16 patients). The adverse drug reactions in patients who discontinued treatment due to adverse drug reactions were nausea in one patient, sleepiness in one patient, gastrointestinal disorder in two patients, and constipation in one patient, with one of the three patients discontinuing treatment due to more than one adverse drug reaction.

The incidence of adverse drug reactions in the control group was 50% (10/20 patients), and the breakdown of the adverse drug reactions were as follows: nausea in four patients, sleepiness in three patients, constipation in two patients, dizziness in

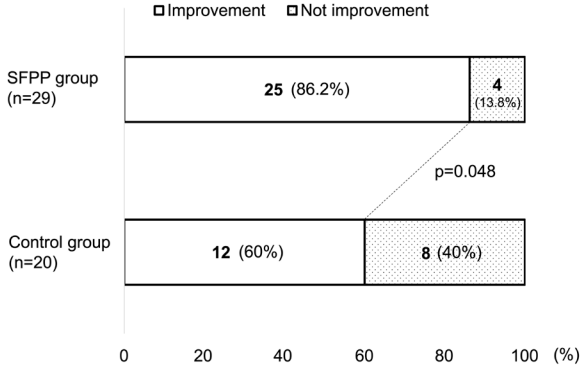

Figure 3. Degree of improvement in VAS score. $p < 0.05$ Fisher's exact test.

two patients, stomatitis in one patient, diarrhea in one patient, impaired urination in one patient, and headache in one patient. The treatment continuation rate was 45%, and reasons for discontinuation were adverse drug reactions in six patients, worsening in one patient, no change in two patients, and unknown in two patients. The treatment discontinuation rate among patients who developed adverse drug reactions was 60% (6/10 patients). Adverse drug reactions in patients who discontinued treatment due to adverse drug reactions were nausea in three patients, sleepiness in one patient, constipation in two patients, dizziness in one patient, stomatitis in one patient, diarrhea in one patient, impaired urination in one patient, and headache in one patient, with four of the six patients discontinuing treatment due to more than one adverse drug reaction.

There was no significant difference in the incidence of adverse drug reactions including gastrointestinal disorder and skin disorder due to plasters between the two groups (Table 3). In the SFPP group, oral NSAIDs were not concurrently used. Therefore, preventive

stomach medicines were not prescribed. In the control group, however, stomach medicines were prescribed for patients who were using oral NSAIDs, and the proportion of patients who were taking stomach medicines was significantly higher at 70%.

The treatment continuation rate was significantly higher in the SFPP group than in the control group, and the treatment discontinuation rate due to adverse drug reactions was significantly lower in the SFPP group than in the control group (Table 4).

Table 3. Adverse drug reaction data

Items	SFPP group (n = 29)	Control group (n = 20)	p
None	12 (41.4%)	9 (45.0%)	1.000
Gastrointestinal disorder	5 (17.2%)	0 (0%)	0.070
Skin disorder	1 (3.4%)	0 (0%)	1.000
Headache	0 (0%)	1 (5.0%)	0.408
Thirst	1 (3.4%)	0 (0%)	1.000
Sleepiness	6 (20.7%)	3 (15.0%)	0.720
Nausea	7 (24.1%)	4 (20.0%)	1.000
Constipation	1 (3.4%)	2 (10.0%)	0.559
Eyelid edema	0 (0%)	0 (0%)	-
Stomatitis	0 (0%)	1 (5.0%)	0.408
Impaired urination	0 (0%)	1 (5.0%)	0.408
Dizziness	0 (0%)	2 (10.0%)	0.162
Diarrhea	0 (0%)	1 (5.0%)	0.408
Unknown	1 (3.4%)	1 (5.0%)	1.000

Data are n (%). N.S., Fisher's exact test. SFPP: S-flurbiprofen plaster.

4. Discussion

Chronic pain is believed to have two disease states: one in which a noxious stimulus is continuously or repeatedly acting, and one in which a spontaneous pain continues even though there is no finding of tissue injury or the healing of tissue injury. The former is mainly nociceptive pain, which often responds to NSAIDs and surgical therapy. The latter often becomes involved with psychosocial factors. Therefore, NSAIDs and surgical therapy are ineffective in the elimination of pain (*15*). In addition, acute pain often occurs repeatedly during the course of chronic pain, which complicates the pathology (*6*).

According to a national questionnaire survey on the influence of chronic pain on ADL in 40,000 men and women 20 years of age or older, in all questions about ADL, 20%-30% of respondents replied that chronic pain always or often influences ADL, indicating that the impairment of ADL frequently occurs (Figure 4) (*3*).

Regarding the relationship between chronic pain and mortality, there is a report that patients 50 years of age or older who have pain in broad areas of the

Table 4. Continuation rate data

Items	SFPP group (n = 29)	Control group (n = 20)	p
Continuation/treatment termination due to improvement	22 (75.9%)	9 (45.0%)	0.038‡
Other reasons for treatment termination	7 (24.1%)	11 (55.0%)	
Adverse drug reaction	3 (10.3%)	6 (30.0%)	
Worsened	1 (3.4%)	1 (5.0%)	
Unknown	3 (10.3%)	2 (10.0%)	
Unchanged	0 (0%)	2 (10.0%)	

Data are n (%). ‡$p < 0.05$ Fisher's exact test. SFPP: S-flurbiprofen plaster.

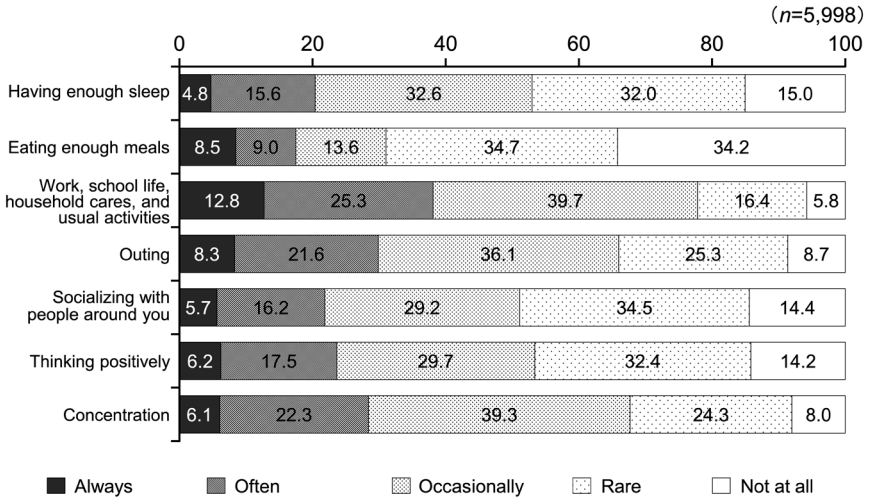

Figure 4. Influences of chronic pain on ADL. National survey in men and women 20 years of age or older (the number of respondents: first survey, n = 41,597; second survey, n = 5,998). Shoji Yabuki *et al.* Clinical Orthopaedic Surgery. 2012; 47:127-134.

locomotorium have high mortality, from cancer in particular (*4*). Also, in a report that pain in the locomotorium and death were correlated, the highest mortality occurred when pain was in the lower back, followed by pain in the hip joint and neck (*5*).

As mentioned above, chronic pain impairs many ADLs and raises mortality. Conditions derived from chronic pain not only worsen the physical function of the patient, but also induce an unhealthy mental state. Moreover, iatrogenic problems due to the treatment of chronic pain, such as adverse drug reactions and complications of invasive treatment, also increase distress. In patients with severe chronic pain, the mixing of chronic with acute pain make the condition refractory, which unfortunately induces some patients to commit suicide.

Due to the complexity of the pathology of chronic pain, treatment methods vary. In clinical practice, a combination of drugs is used according to Clinical Practice Guidelines for the Management of Chronic Pain with careful attention to adverse drug reactions. In the present study, pharmacotherapy using a combination of DLX and SFPP or conventional NSAIDs was performed.

Since reducing chronic pain due to OA and terminating the treatment early should be important to QOL improvement, I evaluated factors associated with the termination of treatment due to the improvement of symptoms. The results showed that women were significantly more likely than men to terminate treatment and the SFPP group was significantly more likely than the control group to terminate treatment. As a cause of the former result, it was reported that the tendency to develop depression is stronger in elderly women than elderly men and depression is related to sex differences in pain (*16*). It is presumed that oral DLX improved depression. Among the causes of the latter result are (a) improvement in the course of VAS score in the SFPP group compared to the control group up to nine months from the start of treatment and (b) significantly higher VAS score improvement rate.

When the efficacy data were compared, there was no significant difference in change in VAS score over time between the two groups, but significant improvement one month after the start of treatment in both groups. Only the SFPP group, however, showed significant improvement compared to the start of treatment between three months and nine months after the start of treatment. Moreover, the proportion of patients whose VAS score was improved was significantly higher in the SFPP group, and the proportion of patients whose VAS score was worsened or unchanged was significantly higher in the control group. Although short-term outcomes between these two groups did not differ, on the basis of these results, I thought that long-term outcomes might be better in the SFPP group. Even in the SFPP group, however, no significant improvement was observed 12 months or later after the start of treatment. This indicates that pain in patients who continue to receive analgesics may not be improved because a characteristic of analgesic treatment is that it is terminated when pain is improved.

Reasons for the significantly higher treatment continuation rate in the SFPP group is thought to solve the polypharmacy problem by prescribing plasters instead of oral drugs, which results in no increase in the number of orally administered drugs, and the comparability of the analgesic effect of SFPP to that of conventional NSAIDs. The efficacy of SFPP was supported by a study comparing the pharmacokinetics of SFPP and oral NSAIDs, which showed that SFPP concentrations in the synovium and the synovial fluid started to rise more slowly, but were maintained at high levels longer than NSAIDs concentrations (*17*), and by a study which confirmed the efficacy of SFPP irrespective of the concurrent use of oral NSAIDs (*18*).

When safety data were compared, there was no significant difference in the incidence of adverse drug reactions between the two groups. There was also no significant difference in the incidence of gastrointestinal disorder. The proportion of patients who were taking preventive stomach medicines, however, was significantly higher in the control group, so I thought the incidence of gastrointestinal disorder may have been suppressed in the control group. The treatment discontinuation rate due to adverse drug reactions was significantly lower in the SFPP group than in the control group, 19% and 60%, respectively. I thought that this was because the number of serious adverse drug reactions requiring the discontinuation of treatment was small in the SFPP group. There is also a report that the frequency of adverse drug events in elderly inpatients was significantly higher among those taking six oral drugs or more than among those taking five drugs or fewer (*19*). This led me to believe that no increase in the number of oral drugs and the solution of the polypharmacy problem influenced the treatment discontinuation rate in the SFPP group. While both (a) the incidence of gastrointestinal disorder associated with SFPP administration may be lower than with oral NSAIDs administration (*20*) and (b) the risk cardiovascular or renal disorder is not worrisome as an adverse drug reaction to SFPP (*21*) have been reported, there is also a report to the effect that the risk of NSAIDs use is similar whether topically or orally administered (*22*). Therefore, NSAIDs need to be administered more cautiously in patients with cardiovascular disease and renal disorder.

Limitations of the present study are as follows: this was a retrospective study with a small number (only 49) of patients; of the OA, lumbar spondylosis was not included; and there was a significant difference in the proportion of patients who were taking stomach medicines between the two groups.

5. Conclusions

In the present study, treatment outcomes for chronic pain due to OA were compared between two combination therapies: (a) DLX and SFPP and (b) DLX and conventional NSAIDs. The results showed that women (compared to men) and the SPFF group (compared to the control group) were significantly more likely to terminate treatment due to the improvement of symptoms. Time to the termination of treatment due to the improvement of symptoms tended to be shorter in the SFPP group, but the difference between the two groups was not significant. VAS scores in the SFPP group were significantly improved one month later and showed significant difference up to nine months later, while VAS scores in the control group were significantly improved one month later, but did not show significant difference after that. Regarding the VAS score improvement rate, moreover, the proportion of improved and somewhat improved patients was significantly higher in the SFPP group than in the control group, suggesting that the combination therapy of DLX and SFPP had higher efficacy than the combination therapy of DLX and conventional NSAIDs.

Although there was no significant difference in the incidence of adverse drug reactions between the two groups, the treatment discontinuation rate due to adverse drug reactions was significantly higher in the control group than in the SFPP group. Although no significant difference was seen between the control group and the SFPP group, skin disorder due to plasters was reported in the SFPP group, and I thought that appropriate management of this disorder would be needed. In the control group, since a significantly higher proportion of patients were taking preventive stomach medicines, I thought that the incidence of gastrointestinal disorder may have been suppressed in the control group.

It was suggested that the efficacy of combination therapy with DLX plus SFPP for chronic pain due to OA is equal to or higher than that of DLX plus conventional NSAIDs, and therefore that DLX plus SFPP can also be an effective option in terms of adverse drug reactions and polypharmacy.

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