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Effects of Pentosan Polysulfate in Osteoarthritis of the Knee: A Randomized, Double-Blind, Placebo-Controlled Pilot Study

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ABSTRACT

Background: Recent recommendations from the Group for the Respect of Excellence and Ethics in Science for the clinical assessment of the effects of disease-modifying osteoarthritis (OA) drugs suggest that improvement in joint space narrowing, pain, and function relative to a control group should be the primary end points.

Objective: The aim of this study was to assess the ability of sodium pentosan polysulfate (NaPPS) to improve pain and function in patients with OA of the knee.

Methods: This randomized, double-blind, placebo-controlled pilot study was performed at the Queen Elizabeth II Medical Centre, Perth, Australia. Patients aged ≥18 years with OA of the knee were randomly assigned to receive NaPPS 3 mg/kg or Ringer's solution (control), IM QW for 4 weeks. Efficacy was assessed at enrollment and weekly during the 4 weeks of treatment and at weeks 8, 12, 16, and 24. Seven direct clinical assessments were made, including intensity of early morning joint stiffness, pain at rest, and pain on walking. A 10-cm visual analog scale (VAS) was used to assess pain at rest and on walking and early morning joint stiffness. *Response* was defined as a change from baseline in VAS score ≥2 cm. Function was assessed using the 10-cm VAS to rate 13 activities of daily living (ADLs), including stair climbing and domestic chores. Patient global assessment of the overall effectiveness of the study drug comprised a 4-point Likert scale (0 = not effective to 3 = maximally effective). An aggregate score for all ADL functions was calculated as the mean change from baseline score of all of the ADLs as determined at 4, 8, 12, 16, and 24 weeks after commencement of the study. For tolerability monitoring, hematology and biochemistry were used, and patients were questioned about adverse events at each visit.

Results: A total of 114 patients were enrolled (83 women, 31 men; mean [SD] age, 63.3 [1.5] years; NaPPS group, 54 patients; control group, 60 patients). Sig-

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nificant differences in scores of 3 of the 7 direct clinical assessments were found between the 2 groups (duration of joint stiffness at 4, 8, 12, and 16 weeks [all, $P \leq 0.015$]; pain at rest at 8, 12, 16, and 24 weeks [all, $P \leq 0.017$]; and patient global assessment at 4, 8, 12, 16, and 24 weeks [all, $P \leq 0.006$]). The rates of trial continuation were higher in the NaPPS group compared with those in the control group at 8, 12, and 24 weeks (all, $P < 0.05$). Mean scores for 3 of 13 ADLs were significantly higher in the NaPPS group compared with those in the control group at weeks 8 and 12 (all, $P \leq 0.03$). On combining all of the ADL scores, functional improvement from baseline was found at weeks 8 and 12 in the NaPPS group (both, $P = 0.02$). Mild bruising at the injection site occurred in <1% of patients in both treatment groups.

Conclusions: In this pilot study, 4 weekly injections of NaPPS were associated with significantly improved duration of joint stiffness and pain at rest compared with controls for 20 weeks after the cessation of treatment, and significantly improved pain on walking and overall function for 8 weeks after the cessation of treatment in these patients with OA of the knee. (*Curr Ther Res Clin Exp.* 2005;66:552–571)

Key words: osteoarthritis, pentosan polysulfate, symptomatic relief.

INTRODUCTION

Osteoarthritis (OA) is the most prevalent type of arthritis, affecting >16 million individuals aged >65 years in the United States and ~70% worldwide.[1–3] In addition to the pain and disability associated with OA, enormous social and economic consequences are augmented as the longevity of the population increases.[4–6]

OA is a multifactorial disorder in which aging, genetic, hormonal, and mechanical factors are all important contributors to disease onset and progression. OA emerges as a clinical syndrome when these etiologic determinants converge, resulting in a level of joint injury sufficient to impair function and cause stiffness and pain. These clinical symptoms are accompanied by radiologic evidence of joint space narrowing (JSN), subchondral bone sclerosis, and osteophytosis at the joint margins.[3] The breakdown of articular cartilage in joints affected by OA results in the release of detritus and molecular fragments derived from the extracellular matrix into the synovial cavity. Because these entities are antigenic, they elicit a secondary synovitis.[7]

In addition to analgesics, the agents most frequently used to treat OA are the steroidal and nonsteroidal anti-inflammatory drugs (NSAIDs). However, these drugs mainly relieve the symptoms of OA and exhibit negligible beneficial effects on the underlying pathology and/or disease progression.[8,9] In fact, some reports suggest that some NSAIDs might exacerbate the failure of cartilage and bone in arthritic joints by inhibiting cellular repair mechanisms and connective tissue homeostasis.[8,9] Also, long-term use of NSAIDs has been associated with serious adverse effects in the elderly population, including a high risk for gastrointesti-

nal lesions arising from NSAIDs' inhibitory activity on the synthesis of the gastroprotective prostaglandins by the cyclooxygenase (COX)-1 enzymatic system.[10,11] Although newer NSAIDs with selective COX-2 inhibitory activity have been associated with a reduced risk for gastrointestinal adverse events, long-term, controlled studies have found an increased risk for thrombosis and myocardial infarction associated with their use in susceptible patients with OA.[12–14]

In the past few decades, the concept of disease- (or structural-) modifying OA drugs (DMOADs) have been explored as an alternative treatment modality for OA.[15,16] Such agents were defined by their ability to slow down, arrest, or reverse OA disease progression over time. From the standpoint of drug-regulatory agencies, DMOADs would be required to reduce the rate of cartilage loss in the affected joint, as might be measured by decreased JSN. However, this structural change in cartilage would need to correlate with improved symptoms.[17] Time to total joint replacement has been suggested as an alternative efficacy end point and a possible index of positive clinical outcome of DMOAD treatment.[17] However, 1 report concluded that time to total joint replacement was not an acceptable primary efficacy end point because it lacked specificity.[18]

Pentosan polysulfate (PPS) is a semisynthetic drug manufactured from Beechwood hemicellulose by sulfate esterification of the sugar ring hydroxyl groups. It has a mean molecular weight (MW) of 5700 Da and a sulfur content of ~16%.[19] The results from numerous in vitro and animal studies of the polyanion sodium PPS (NaPPS) have led to the suggestion that this agent might be classified as a DMOAD because of its ability to preserve the integrity of the articular cartilage and bone while improving the quality of the joint synovial fluid.[19–21] Thus, NaPPS supports chondrocyte and fibroblast anabolic activities while attenuating catabolic events associated with destruction of the cartilage extracellular matrix.[21] Although some of the anticatabolic activities of NaPPS have been shown to occur via direct inhibition of enzymes such as elastase, cathepsin-B, and hyaluronidase,[20,21] this drug can enter chondrocytes and fibroblasts, bind to promoter proteins in the nucleus, and down-regulate gene expression of matrix metalloproteinases.[21] These chondroprotective activities of NaPPS have been demonstrated to be effective in rat, rabbit, and canine models of OA.[20,21] Moreover, the biosynthesis of high-MW hyaluronan by synovial fibroblasts, which is diminished in OA joints, was restored when these cells were incubated with NaPPS in vitro or after its intra-articular injection into joints of patients with OA.[21]

Despite these laboratory findings, clinical studies to support the classification of NaPPS as a DMOAD are lacking. Based on recommendations from the Group for the Respect of Excellence and Ethics in Science, Liege, Belgium,[17,18] to assess NaPPS as a clinically efficacious DMOAD requires a placebo-controlled, double-blind clinical trial of sufficient duration to allow changes in JSN to be reliably determined and correlated with improved symptoms. Recent reports have suggested that patients with OA recruited into DMOAD clinical trials

would need to be monitored clinically and radiographically for at least 24 months.[22,23] However, even if such a trial were implemented, the accuracy of the radiologic method of assessment could still be questioned without an assessment of symptom improvement.[24]

The objective of this preliminary study was to assess the effectiveness and tolerability of NaPPS in patients with OA of the knee.

PATIENTS AND METHODS

Study Design

This randomized, double-blind, placebo-controlled pilot study was conducted at the Queen Elizabeth II Medical Centre, Perth, Australia. The protocol was approved by the Human Research Ethics Committee at the center.

Inclusion and Exclusion Criteria

Patients were recruited from outpatient rheumatology clinics and databases of rheumatologists in private practice by a letter of request from the chief clinical investigator (J.E.). Inclusion criteria were age ≥18 years, OA of 1 or both knees (the grade of OA was determined radiographically using the classification criteria of Kellgren and Lawrence[25]), symptomatic pain at rest and on walking and moderate early morning joint stiffness (scores ≥4 on a 10-cm visual analog scale [VAS] [0 = no difficulty or pain to 10 = worst imaginable difficulty or pain]), willingness to attend follow-up visits, and mild changes on radiography indicative of OA using the Kellgren and Lawrence[25] criteria. Patients were excluded if they had any other rheumatic condition that would interfere with assessment (eg, rheumatoid arthritis or OA of any other lower limb joint, such as the ankle), had current bleeding diathesis or were receiving treatment with warfarin, had any other severe condition affecting mobility (eg, cardiac or respiratory disease), had severe changes on radiography indicative of OA, and/or were receiving prednisolone or were unable to discontinue treatment with NSAIDs for any reason. All eligible patients provided written informed consent to participate.

Study Drugs

After an NSAID washout period of 2 weeks, patients were randomized, in a 1:1 ratio using a computer-generated table of random numbers, to receive NaPPS 3 mg/kg or Ringer's solution (control). The NaPPS was provided in sterile, injectable vials at a concentration of 100 mg/mL, diluted in water to a volume of 10 mL. To maintain blinding of the investigators and patients, the Ringer's solution was provided at a similar volume in identical vials. All injections were administered into the gluteal muscle region of each patient at 1-week intervals for 4 weeks (**Figure 1**). NSAID use was not allowed throughout the study.

Patients were allowed to use rescue medication (paracetamol [acetaminophen]) when they considered the joint pain to be unbearable. At each

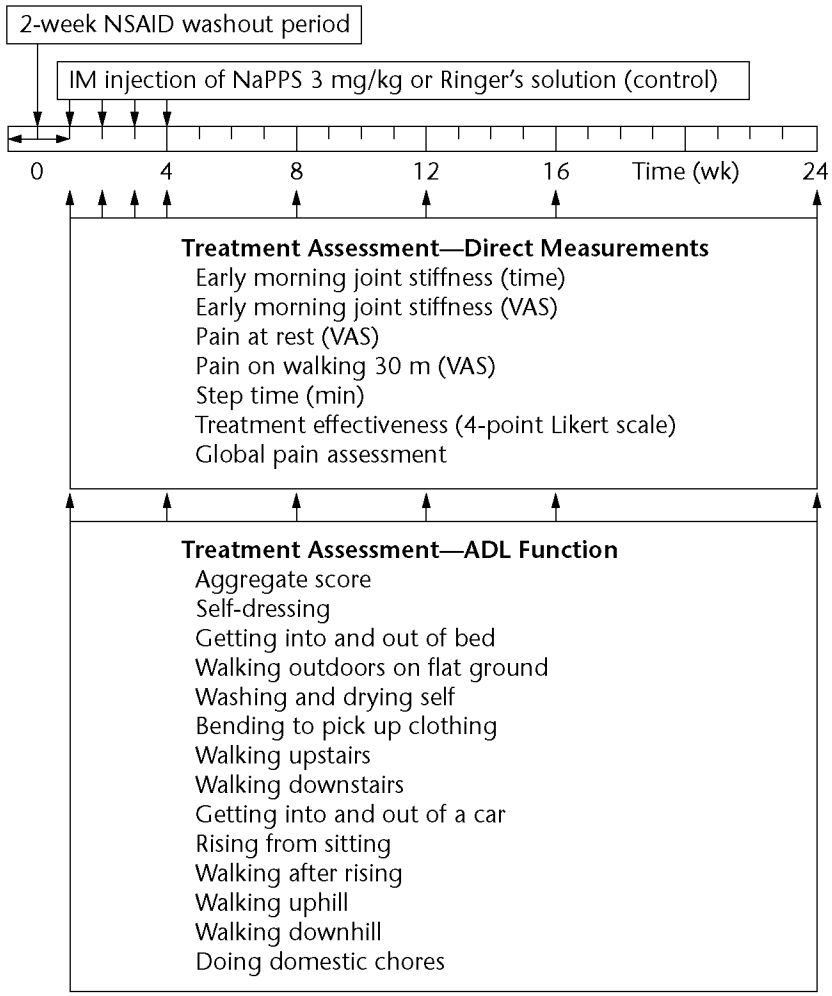

Figure 1. Study protocol and timeline used for treatment and assessment in the sodium pentosan polysulfate (NaPPS) osteoarthritis clinical trial. VAS = 10-cm visual analog scale (0 = no difficulty or pain to 10 = worst imaginable difficulty or pain); ADL = activities of daily living.

visit, patients were questioned concerning their consumption of NSAIDs or paracetamol.

Efficacy Assessments

The primary end points in this study were improvement in pain and function. Patient assessments included 7 direct clinical measurements, patient global assessment, and assessment of function in 13 activites of daily living (ADLs).

The direct clinical measurements obtained using the 10-cm VAS included intensity and duration of early morning joint stiffness, pain at rest, pain on walking, and treatment effectiveness.

Patient global assessment of the overall effectiveness of the study drug comprised a 4-point Likert scale (0 = not effective to 3 = maximally effective).[26] All assessments were made at each weekly visit during the 4 weeks of treatment and at weeks 8, 12, 16, and 24.

Each patient completed an ADL function assessment questionnaire consisting of 13 parameters, including stair climbing and domestic chores, modified from the Western Ontario and McMaster (WOMAC) University Osteoarthritis Index.[26] An aggregate score for all ADL functions was calculated as the mean change from baseline score on all of the ADLs as determined at 4, 8, 12, 16, and 24 weeks after commencement of the study.

Clinically important improvement was defined a priori to identify patient characteristics that might predict who would respond to NaPPS treatment at 4 weeks. A relevant response for each parameter was indicated by a ≥2-cm change from baseline in VAS scores for early morning joint stiffness, pain at rest, and pain on walking in all affected joints, and a patient global assessment of 3 (maximum treatment effectiveness).

Tolerability Assessments

For tolerability monitoring, nonfasted blood samples were collected at baseline and at study weeks 4 and 12. Blood was subjected to standard laboratory hematologic (full blood count) and biochemical (kidney and liver function) analysis. In addition, patients were questioned about adverse events (eg, injection site reaction, rash, nausea) at each visit.

Statistical Analysis

A power analysis determined that to achieve 80% power at an alpha level of 5%, we would need 180 patients (90 per group) to show a 20% improvement in VAS scores for the primary end points. However, in an interim analysis, the response was sufficiently strong in the NaPPS group to suggest that statistical significance could be achieved with <180 patients. One hundred fourteen patients were included in the analyses.

The number of patients remaining in the study at each visit was recorded, and the data were analyzed on an intent-to-treat (ITT) basis, with the last record being carried forward in the event of loss to follow-up. The ITT analysis was performed to adjust for the differential withdrawal rate. Baseline characteristics were compared between the 2 groups (NaPPS and control) using the χ^2 and Mann-Whitney U statistics for categoric and quantitative data, respectively. Nonparametric tests were used because data were not normally distributed. Changes from baseline in VAS or patient global assessment scores were compared using the Student t test (unpaired, 2-tailed). Response rates were compared using the 2-tailed Z test for proportions. Differences were considered to be statistically significant at $P \leq 0.05$.

RESULTS

One hundred fourteen patients were enrolled (83 women, 31 men; mean [SD] age, 63.3 [1.5] years). The demographic profiles of the 2 treatment groups, consisting of 54 and 60 patients in the NaPPS and control groups, respectively, are shown in **Table I**. On breaking the randomization codes, no significant differences in age, sex, body mass index (BMI), number of involved joints (hips or knees), global pain score, or radiographic grade of knee OA were found between the 2 groups (**Table I**). However, the between-group difference in the mean (SE) duration of OA symptoms was significant (NaPPS, 5.0 [0.5] years; controls, 6.8 [0.7] years [$P = 0.03$]). There were no significant between-group differences in rates of ADL functional disability assessed at baseline (**Table II**). All 114 patients completed the 4-week course of injections (weeks 1–4), but some patients were withdrawn from the study due to dissatisfaction with treatment or loss to follow-up (NaPPS, 24; control, 40). The percentages of patients remaining in the trial were significantly higher in the NaPPS group at 8, 12, and 24 weeks compared with controls (mean [SE]: NaPPS, 85.2% [4.8%], 61.1% [6.6%], and 55.6% [6.8%], respectively; controls, 65.0% [6.2%], 43.3% [6.4%], and 33.3% [6.1%], respectively [$P < 0.01$, $P < 0.05$, and $P < 0.01$, respectively]) (**Table III**).

Table I. Baseline demographic and clinical characteristics of the study patients.

Parameter	NaPPS (n = 54)	Control (n = 60)
Age, mean (SE), y	62.5 (1.4)	64.0 (1.6)
Sex, no. (%)		
Female	42 (77.8)	41 (68.3)
Male	12 (22.2)	19 (31.7)
BMI, mean (SE), kg/m^2	29.1 (0.7)	29.3 (0.7)
Duration of symptoms		
Mean (SE), y	5.0 (0.5)*	6.8 (0.7)
≤2 y, no. (%) of patients	16 (29.6)	14 (23.3)
≤5 y, no. (%) of patients	35 (64.8)	31 (51.7)
No. of joints affected		
Total	87	89
Mean per patient	1.6	1.5
% Global pain VAS score ≥4, no. (%) of patients	9 (16.7)	17 (28.3)
No. (%) of patients with changes on radiography		
0 Change	0	0
1 Change	18 (33.3)	15 (25.0)
2 Changes	0	0
3 Changes	10 (18.5)	4 (6.7)

NaPPS = sodium pentosan polysulfate; BMI = body mass index; VAS = visual analog scale.
*$P = 0.03$ versus control group.

Table II. Baseline functional disability* in activities of daily living (ADLs) in patients with osteoarthritis.† Values are percentages of patients.

ADL	NaPPS (n = 54)	Control (n = 60)
Walking upstairs	96	93
Walking downstairs	96	92
Walking downhill	94	87
Walking uphill	94	87
Walking immediately after rising	89	92
Getting into and out of a car	89	87
Rising from sitting	89	87
Doing domestic chores	81	77
Getting into and out of bed	67	63
Walking outdoors on flat ground	44	38
Bending to pick up clothing	13	8
Washing and drying self	5	10
Self-dressing	5	5

NaPPS = sodium pentosan polysulfate.
*Score ≥4 on 10-cm visual analog scale (0 = no pain or difficulty to 10 = worst imaginable pain or difficulty).
†No significant between-group differences were found.

Direct Measurement Parameters

The duration of early morning joint stiffness was significantly less in the NaPPS group at weeks 4, 8, 12, and 16 (all, $P \leq 0.015$) (**Figure 2A**). In patients treated with NaPPS whose baseline VAS score for pain at rest was ≥2 cm (ITT population [36 patients]), the mean VAS score did not show discrimination from that in the control group until week 8 ($P = 0.016$), and the VAS reduction of 0.5 lasted at least 16 weeks thereafter (all, $P \leq 0.017$) (**Figure 2B**). On statistical analysis of pain on walking, using the absolute VAS as the control, no statistically significant differences were found at any time point (data not shown). However, using the response rate analysis for VAS score ≥2, a statistically higher proportion of patients had improvement in pain on walking in the NaPPS group (range, 35.2%–50.0%) compared with the control group (range, 16.7%–25.0%) at 4, 12, and 24 weeks ($P = 0.001$, $P = 0.02$, and $P = 0.02$, respectively) (**Table III**).

Patient global assessment of treatment effectiveness was significantly higher in the NaPPS group compared with the control group at all time points after the fourth injection (all, $P \leq 0.006$) (**Figure 3**). The percentage of patients reporting maximal effectiveness was significantly greater in the NaPPS group compared with the control group at all time points (all, $P \leq 0.01$); however,

Table III. Response rates after 4-week administration of sodium pentosan polysulfate (NaPPS [54 patients]) or Ringer's solution (control [60 patients]) in patients with osteoarthritis of the knee. Values are percentages (SE) of patients.

	4 Weeks			8 Weeks			12 Weeks			24 Weeks		
Parameter	NaPPS	Control	*P*	NaPPS	Control	*P*	NaPPS	Control	*P*	NaPPS	Control	*P*
Pain at rest*	40.0 (8.9)	23.3 (6.4)	0.13	30.0 (8.3)	16.3 (5.6)	0.17	26.7 (8.1)	14.0 (5.3)	0.19	16.7 (6.8)	11.6 (4.9)	0.55
Pain on walking*	50.0 (6.8)	23.3 (5.5)	0.001	37.0 (6.6)	25.0 (5.6)	0.16	35.2 (6.5)	16.7 (4.8)	0.02	37.0 (6.6)	18.2 (5.0)	0.02
Joint stiffness*	57.4 (6.7)	23.3 (5.5)	<0.001	50.0 (6.8)	28.3 (5.8)	0.02	44.4 (6.8)	23.3 (5.5)	0.02	44.4 (6.8)	23.3 (5.5)	0.02
Maximal treatment effectiveness†	33.3 (6.4)	5.0 (2.8)	<0.001	29.6 (6.2)	8.3 (3.6)	<0.001	22.2 (5.7)	5.0 (2.0)	0.01	18.5 (5.3)	3.3 (2.3)	0.01
% Remaining in trial	98.1 (1.9)	98.3 (1.7)	0.94	85.2 (4.8)	65.0 (6.2)	<0.01	61.1 (6.6)	43.3 (6.4)	<0.05	55.6 (6.8)	33.3 (6.1)	<0.01

*Response = visual analog scale score ≥2 cm (scale: 0 = no difficulty or pain to 10 = worst imaginable difficulty or pain).
†Score of 3 on patient global assessment (4-point Likert scale: 0 = not effective to 3 = maximally effective).

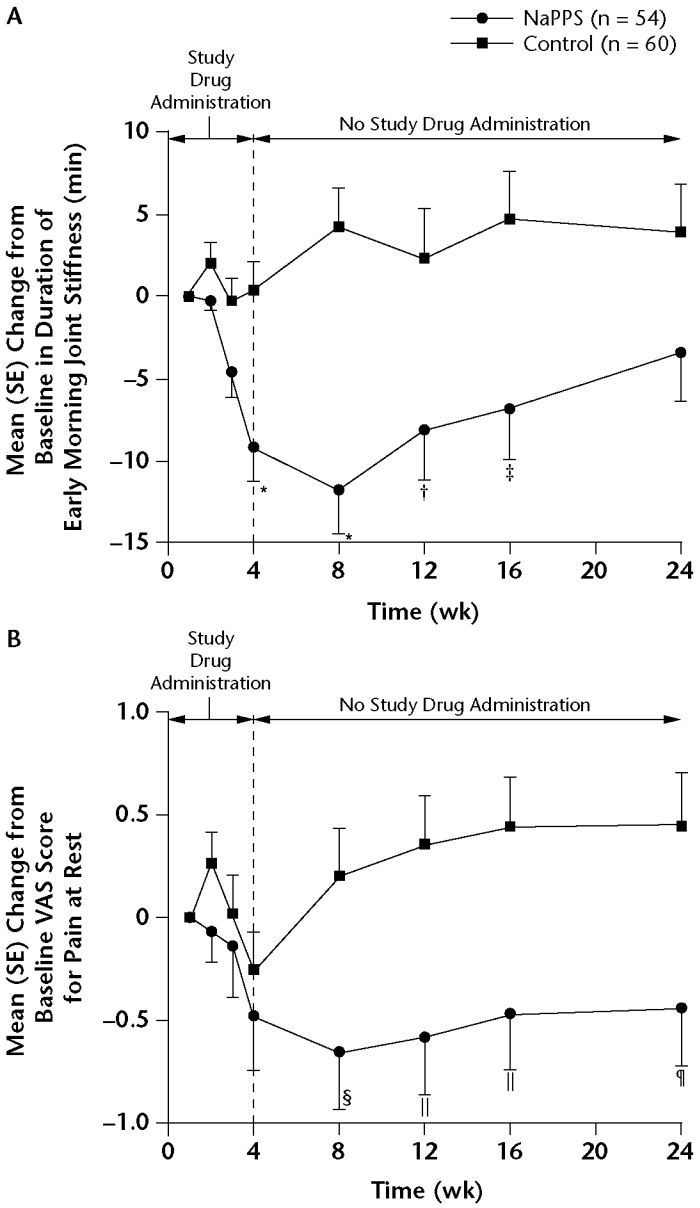

Figure 2. Changes from baseline in (A) duration of early morning joint stiffness and (B) pain at rest on a 10-cm visual analog scale (VAS) (0 = no difficulty or pain to 10 = worst imaginable difficulty or pain) after 4-week administration of sodium pentosan polysulfate (NaPPS) or Ringer's solution (control) in patients with osteoarthritis of the knee. *P* versus control group: *<0.001; †=0.015; ‡=0.008; §=0.016; ‖=0.014; ¶=0.017.

in the NaPPS group, this effect declined from 33.3% at 4 weeks to 18.5% at 24 weeks. In contrast, the rate in the control group was 5.0% at 4 weeks and 3.3% at 24 weeks (**Table III**).

Subanalysis

In the analysis to identify patient characteristics that might predict who would respond to NaPPS treatment at 4 weeks, in the NaPPS-treated group, using treatment effectiveness as a marker of response, statistical analysis found no significant differences in mean age, sex, mean symptom duration, mean BMI, or mean baseline VAS scores for pain on rest and joint stiffness. When *responders* were defined as patients reporting maximum treatment effectiveness, 44.4% of responders had mild radiographic changes (JSN) compared with 33.3% of nonresponders, and 41.7% of responders had Kellgren and Lawrence[25] grade 1 changes on radiography compared with 26.7% of nonresponders; these differences did not reach statistical significance. Furthermore, there was no difference in the percentages of patients in each group whose disease duration was ≤5 years or who were obese (BMI, ≥30 kg/m^2). Using improved pain on walking as a response measure at 4 weeks, no differences in sex, mean age, percentage

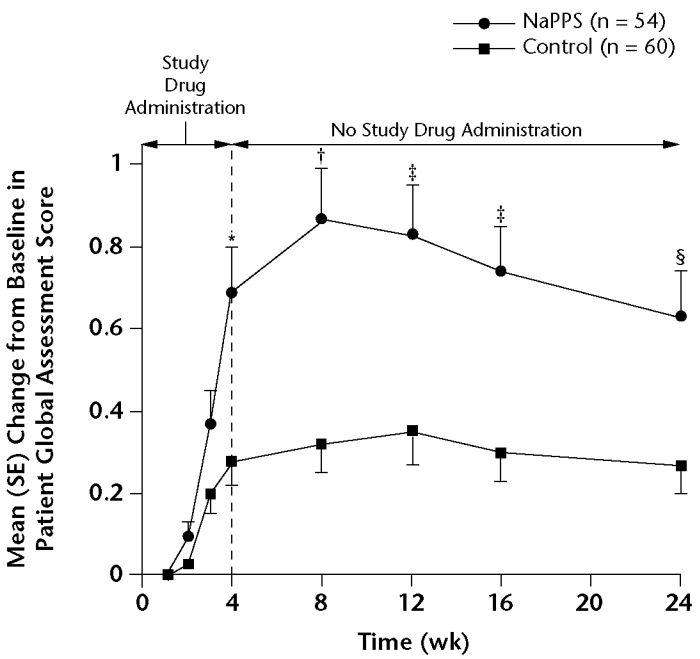

Figure 3. Changes from baseline in patient global assessment score, measured on a 4-point Likert scale (0 = not effective to 3 = maximally effective), after 4-week administration of sodium pentosan polysulfate (NaPPS) or Ringer's solution (control) in patients with osteoarthritis of the knee. *P* versus control group: *=0.002; †<0.001; ‡=0.001; §=0.006.

of patients aged 65 years or older, or mean BMI were found. Although the mean disease duration was numerically less in responders compared with nonresponders (3.9 vs 5.8 years), the difference was not statistically significant.

ADL Function Parameters

Of the ADL functions shown in **Table II**, self-dressing, washing and drying self, and bending to pick up clothing were found to be unaffected by the disease state at baseline (ie, <13% of patients in both groups reported any difficulty at all in undertaking these tasks). For the remaining 10 ADLs, improvements in only 3 ADLs in the NaPPS group were greater compared with those in the control group at 24 weeks.

The mean score for ability to get into and out of bed was significantly higher in the NaPPS group compared with the control group at all time points (all, $P \leq 0.006$) (**Figure 4A**). The mean change from baseline score for walking outdoors on flat ground was significantly higher in the NaPPS group compared with that in the control group at all time points (all, $P \leq 0.013$) (**Figure 4B**). Improvements in scores for walking downhill were significantly greater in the treated group 4 and 8 weeks after cessation of treatment compared with controls ($P = 0.02$ and $P = 0.03$, respectively) but not at weeks 16 or 24 (**Figure 4C**). There were no significant between-group differences in the other 4 walking ability assessments (walking immediately after rising, walking uphill, walking upstairs, and walking downstairs), difficulty rising from sitting, or difficulty doing domestic chores (data not shown).

When all of the ADL function assessments were aggregated into a single functional score (as change from baseline), the mean aggregate change from baseline score was significantly higher in the NaPPS group compared with the control group at 8 and 12 weeks (both, $P = 0.02$) (**Figure 4D**).

Tolerability

No evidence of hematologic or biochemical abnormalities were identified on analysis of blood samples before or after trial end (data not shown). Mild bruising at the injection site occurred in <1% of patients in each treatment group. No other adverse effects were recorded.

DISCUSSION

The results of this pilot study suggest that under controlled, double-blind conditions, 4 consecutive weekly IM injections of NaPPS 3 mg/kg improved joint stiffness, pain at rest, and patient assessment of the effectiveness of treatment for up to 20 weeks after treatment cessation, and pain on walking (as a frequency of response in patients with VAS score ≥2 cm) for 4, 12, and 20 weeks after treatment cessation. The aggregate ADL function scores were also significantly improved at weeks 8 and 12 for the group administered NaPPS. These findings suggest that the drug could improve functional disability in OA.

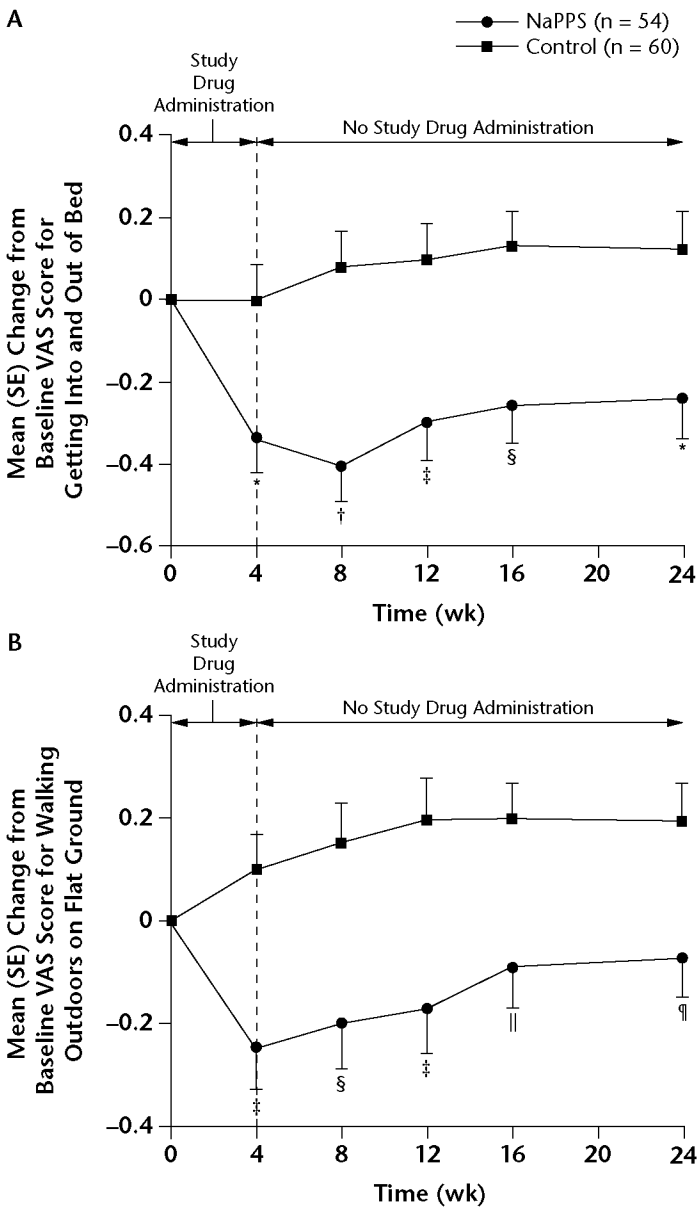

Figure 4. Changes from baseline in function performing activities of daily living, measured on a 10-cm visual analog scale (VAS) (0 = no difficulty or pain to 10 = worst imaginable difficulty or pain) for (A) getting into and out of bed and (B) walking outdoors on flat ground. NaPPS = sodium pentosan polysulfate. *P* versus control group: *=0.006; †<0.001; ‡=0.002; §=0.003; ‖=0.009; ¶=0.013. (continued)

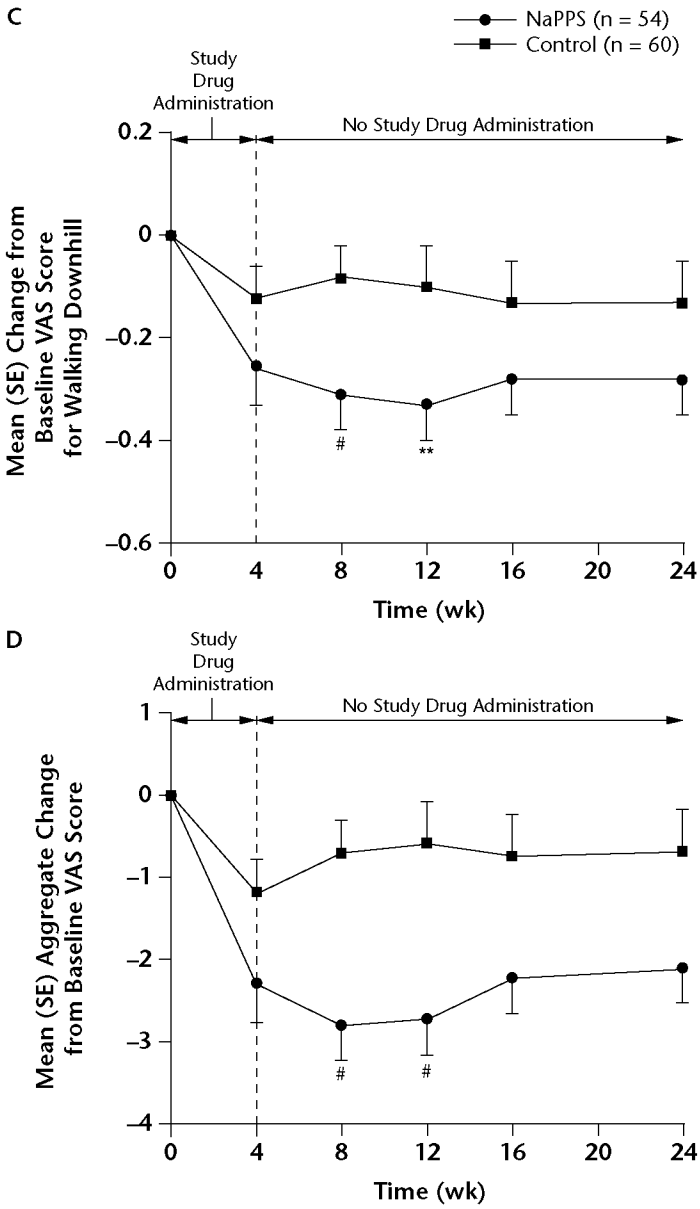

Figure 4. (Continued) Changes from baseline in function performing activities of daily living, measured on a 10-cm visual analog scale (VAS) (0 = no difficulty or pain to 10 = worst imaginable difficulty or pain) for (C) walking downhill and (D) aggregate of all functional scores after 4-week administration of sodium pentosan polysulfate (NaPPS) or Ringer's solution (control) in patients with osteoarthritis of the knee. *P* versus control group: #=0.02; **=0.03.

Although the effectiveness of the drug in reducing walking pain was significant only at 4, 12, and 24 weeks after the end of NaPPS treatment in the frequency of response analysis, examination of the ADL outcomes indicated that the NaPPS-treated patients were generally more active and therefore might be subjecting their joints to more weightbearing stresses compared with before treatment. When overall treatment effectiveness and pain on walking were used as markers of response to therapy, the data suggested that patients with short (<5 years) disease duration and grade 1 radiographic changes in their knee joints responded better to NaPPS treatment compared with patients with more severe disease. However, additional studies are required to confirm this finding. In addition, the study was likely underpowered statistically: power calculations using the validated WOMAC OA scoring system[26] indicated that for an improvement ≥2 cm on the VAS, 80 patients would be needed in each group.

Because NaPPS is not an analgesic and is cleared from the plasma within 12 hours and from body tissues within a few weeks of administration,[21] we can suggest that the symptom relief reported by patients for up to 20 weeks after the end of administration might have been related to NaPPS modification of some aspects of OA pathobiology associated with clinical symptoms. This suggestion is consistent with those from laboratory and animal model studies[19–21] that found that NaPPS was associated with reduced joint inflammation, improved blood flow in subchondral bone and soft tissues, and preserved proteoglycan and hyaluronan concentrations in articular cartilage and synovial fluid.[21]

The anti-inflammatory activity of NaPPS was first reported by Kalbhen[27] using a rat model. Based on the findings, this investigator suggested that the anti-inflammatory activity of NaPPS was largely mediated by its ability to restabilize "leaky" peripheral vasculature and improve microcirculation in the tissues of affected joints. Anticomplement activity and a subsequent reduction in humoral mediators of inflammation were later reported in 16 patients with hypercomplementemia,[28] defined as blood total fatty acid esters >746 mg/dL and total cholesterol >365 mg/dL and in rabbits with myocardial injury administered NaPPS 100 mg IM.[29]

In another study, 15 elderly patients with high blood viscosity and filterability were markedly improved with the use of NaPPS 50 mg IM BID.[30] However, it was reported that the metabolism of ^{14}C-arachidonic acid cultured with leukocytes isolated from the blood of these patients was modified by the drug. Seven days after NaPPS administration, the concentrations of arachidonic acid–derived lipoxygenase (LOX) metabolites released from these cells were significantly lower compared with before treatment. In contrast, arachidonic acid metabolites generated by the COX pathway were increased. The reduced levels of LOX metabolites produced by the leukocytes in patients treated with NaPPS could be associated with diminished production of leukotrienes, such as 5HETE, diHETEs, and LTB_4. LTB_4 is a particularly potent proinflammatory mediator stimulating neutrophil adhesion, chemotaxis, and degranulation.[31] In addition, LTB_4 can induce the synthesis of interleukin-8 and platelet-activating factor,

which can also perpetuate the inflammatory process.[31,32] In addition to their proinflammatory effects, leukotrienes also promote vasoconstriction and vascular permeability.[32] In the study in elderly patients mentioned earlier, Freyburger et al[30] found that the elevated production of prostaglandin concentrations by leukocytes in these patients treated with NaPPS might not have been the result of a stimulatory effect of NaPPS on the COX enzymes directly, but instead might have occurred by "shunting" of the arachidonate metabolism into this pathway after inhibition of the LOX cascade. Regrettably, the investigators in that 1987 study did not report which prostaglandins were elevated during treatment.[30] Therefore, it is not possible to determine whether the effects of NaPPS were selective or influenced by both COX-1 and COX-2. If COX-1 production was enhanced, NaPPS could possibly confer some gastrointestinal protection.[32]

Although down-regulation of inflammatory mediators within the tissues of joints affected by OA could account for some of the useful clinical effects noted in the present study, NaPPS also exhibits other pharmacologic activities that could be just as significant.

PPS has been used in Europe for >40 years as a thromboprophylactic and antilipidemic agent.[33] The literature accumulated over that time has indicated that pentosan mobilizes vascular occlusions by promoting fibrinolysis, reducing fibrinogenesis, and clearing plasma lipids by stimulating lipase release by the endothelium.[20,21]

Intravascular lipid and thrombi have been reported to be often present in the arterial and venous microvasculature of heads of femur removed at the time of total joint replacement surgery for OA.[34,35] The venous stasis and hypertension resulting from the presence of these emboli in OA joints have been reported to be associated with bone ischemia and osteonecrosis.[36,37] These pathologic events have been cited as possible causes of pain in OA, and the aim of early surgical treatment of OA was to release the arterial pressure by fenestration of the subchondral compartment of the affected joint.[38,39]

The antilipidemic and profibrinolytic effects of NaPPS have been reported in a group of 11 postmenopausal women with mild to moderate OA.[40] In that study, the lipolytic parameters were monitored before drug treatment and 8 and 24 hours after they received the first of 4 weekly IM injections of NaPPS 3 mg/kg. Plasma concentrations of lipoprotein lipase, hepatolipase, and superoxide dismutase were significantly elevated between 2 and 4 hours after drug administration.[40] NaPPS treatment was associated with modifications in peripheral blood mononuclear cell procoagulant activity (MPA) and differential leukocyte counts. Patients' MPA, which before drug treatment was higher compared with those in non-OA controls, was significantly reduced to within the normal range 24 hours after NaPPS administration. This effect was maintained for 4 weeks after the end of administration of the drug.[40] Although that clinical study was unblinded, the 11 patients with OA who

completed the course of 4 weekly injections of NaPPS reported significant clinical improvement of their symptoms for up to 12 weeks after the last injection.[41]

In other studies, 2 or more intra-articular 50-mg injections of NaPPS into the joints of 14 patients with rheumatoid arthritis[42] and 28 patients with OA[43] were associated with a clinically significant increase in synovial fluid hyaluronan MW of 70% to 83%, probably resulting from a direct stimulatory effect on synovial fibroblasts.[21,44] The MW and concentration of hyaluronan in the synovial fluid of joints affected by OA are reduced,[45] and the normalization of these parameters by NaPPS could serve to improve the rheologic and cartilage-protective effects of synovial fluid, as has been found with the intra-articular administration of exogenous high-MW hyaluronan.[44] Cartilage hyaluronan and proteoglycans have also been found to be preserved in the joints of animal models of OA after IM administration of NaPPS.[21]

PPS appears to have pharmacologic activities that could be beneficial in OA-affected joint tissues. However, because the metabolic imbalances associated with the pathophysiology of OA are promulgated by etiologic factors (eg, aging, genetic, mechanical) that cannot be directly influenced by the pharmacologic effects of a drug, with time, clinical symptoms might return. The results of the present study suggest that 8 to 12 weeks after the end of drug treatment represents the time frame for the pathology associated with symptoms to become reestablished, but as was expected, this time frame was found to vary from patient to patient.

Although the strength of this study was that it was undertaken using double-blind, randomized conditions, there are limitations to its interpretation, particularly relating to its high withdrawal rate. The study duration was partly addressed by using an ITT analysis. However, there was a considerable between-group difference in loss to follow-up, with a greater proportion of controls not returning. Many of these patients sought other treatments, including joint injections of corticosteroids or hyaluronan, or joint replacement surgery. These patients were considered to be treatment failures.

There were no significant between-group differences in baseline characteristics apart from the mean duration of symptoms, with a difference of 1.8 years. This difference was considered unlikely to be clinically significant in view of the 4 other criteria of disease activity that were statistically similar between the groups. Finally, because the patients were selected volunteers, the results might not be applicable to all patients with OA of the knee.

Further longer-term clinical and radiologic studies are required to confirm these suggestions and to assess the ability of NaPPS to preserve joint articular cartilage, as has been found in animal models of OA.

CONCLUSIONS

In this pilot study, 4 weekly injections of NaPPS were associated with significantly improved duration of joint stiffness and pain at rest compared with con-

trols for 20 weeks after the cessation of treatment, and significantly improved overall function for 8 weeks after the cessation of treatment in these patients with OA of the knee.

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