Effect of glycosaminoglycan polysulfate on chondromalacia patellae

A placebo-controlled 1-year study

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The effect of glycosaminoglycan polysulfate (GAGPS) on damaged patellar cartilage and clinical symptoms of chondromalacia was studied on 31 patients in a placebo-controlled double-blind trial. The clinical diagnosis was confirmed by arthroscopy. The treatment consisted of 12 intramuscular injections of either GAGPS or placebo, and the patients were followed for 1 year. In 26 patients, rearthroscopy was performed at the 1-year follow-up. Comparison of the two arthroscopies showed improvement in 8/13 patients in the GAGPS group compared with 3/13 in the placebo group. The clinical parameters correlated well with the results of the arthroscopies. The results support the use of GAGPS for chondromalacia patellae.

Glycosaminoglycan polysulfate (GAGPS) has been shown to inhibit proteolytic enzymes, which degrade proteoglycans and collagens (Burkhardt and Ghosh 1986, Howell et al. 1986, Altman et al. 1987, Halverson et al. 1987), and has also been shown to increase the rate of synthesis and the degree of polymerization of hyaluronic acid in the synovial fluid (Burkhardt and Ghosh 1986, Howell et al. 1986).

In uncontrolled studies, a good or moderate effect of GAGPS was recorded in the majority of patients with chondromalacia patellae (Paul and Franke 1974, Malze 1983).

We report effects of GAGPS in the treatment of patients with clinical symptoms and arthroscopically verified chondromalacia.

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Patients and methods

Thirty-one consecutive patients of both sexes with patellofemoral pain attending the Sports Clinic at the Deaconess Institute entered the trial. All the patients had given their consent, and the study was endorsed by the local ethics committee. Patient inclusion was done in two steps. Patients with pain during resisted patellar movement underwent arthroscopy. If arthroscopy revealed patellar cartilage lesions, the patient was included in the trial unless there was other joint pathology. Also patients who had used corticosteroids or GAGPS within 40 days or NSAIDs within 7 days of the commencement of the trial were excluded, as were pregnant and nursing mothers, patients under 18 years of age, and patients with any contraindication to GAGPS.

The patients were randomized to either 12 injections of 1 mL GAGPS, 50 mg/mL, (Arteparon®, Luitpold-Werk, Munich) or 12 placebo injections (physiologic saline). The injections were given intramuscularly twice weekly during a 6-week period. The GAGPS and placebo were in all respects indistinguishable and identically packaged, keeping the study strictly double-blind. All the patients were introduced to standardized quadriceps training and told to start the training after the 6-week injection period. The patients were also allowed paracetamol as an escape analgesic.

Table 1. Data for 29 patients with clinical symptoms of chondromalacia patellae and arthroscopically verified damaged patellar cartilage

A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P
GAGPS-treated patients															
1	M/36	175/90	2	2	11	10–0	0––0	2011	2200	2110	0100	3201	0–3	L A2	I
2	M/18	183/90	1	2	2	1–––	20––	212–	101–	200–	000–	301–	21–	L B3	–
3	M/28	181/83	2	2	24	00–0	0000	1111	3100	2100	0100	2101	213	C B1	U
4	F/23	163/56	3	4	6	23–0	23–0	33–0	22–0	22–0	11–0	32–0	0–3	L B1	I
5	M/37	174/68	2	3	36	20–0	2000	3011	2000	2001	1000	2111	323	C B1	I
6	F/18	165/58	2	2	14	0000	0011	2012	2021	2001	2001	3022	310	M B1	U
7	M/38	183/87	1	1	12	0000	2000	3120	2000	2010	2010	2100	313	MC A3	I
8	M/33	171/64	1	4	6	1000	2000	1111	1000	1111	1000	1111	212	M B2	I
9	M/33	167/86	2	4	12	2010	3010	3320	2120	1221	0100	2121	202	M C1	I
10	M/27	176/72	3	1	4	0000	0000	2200	1110	1100	0000	1121	122	C A5	I
11	M/24	185/87	2	4	10	0000	1010	2100	1100	3000	0000	2100	133	C A2	I
12	F/24	153/51	2	3	12	0000	1101	2222	2122	2122	2121	3222	000	M B2	U
13	M/43	177/88	2	3	48	1000	0100	3211	2100	2000	2100	3210	123	C A10	U
14	F/26	178/67	1	4	3	0000	2000	0012	2121	1222	1110	1112	000	C B1	U
Placebo-treated patients															
1	M/35	176/95	2	4	11	3–00	3100	311–	3111	3111	2100	3210	112	C A2	I
2	M/36	172/76	2	4	12	2210	2120	3222	3222	3222	2101	2222	000	C B2	–
3	F/20	16S/57	1	4	7	1000	2000	2001	200–	110–	1000	110–	O32	M B1	I
4	M/32	183/85	2	3	90	1000	1001	2222	0011	2102	0001	1111	000	L A2	U
5	F/22	156/52	1	3	12	–000	0010	2122	2010	3011	0010	1021	201	M B1	U
6	M/29	186/110	2	4	60	1–00	1–00	2–13	1–11	1–11	1–10	2–21	–10	C A4	U
7	F/37	165/72	1	3	5	0000	1000	3110	1000	3010	2000	2110	323	C A2	–
8	M/35	187/84	2	2	60	2001	1002	3113	2002	3003	2002	2113	300	C A10	W
9	M/29	184/88	1	3	7	01––	100–	1111	1122	2212	0100	2112	010	C B3	U
10	M/20	182/80	2	3	48	0010	0011	2102	0112	2112	1011	2122	000	C A2	U
11	M/36	179/80	1	3	6	101–	1110	3121	2111	3212	1001	2212	110	C A1	W
12	M/36	178/79	2	4	8	2002	2002	3123	2012	2113	2012	3223	210	M A3	U
13	M/20	185/70	2	2	6	0000	2001	3002	2102	3002	2000	3102	221	C B2	W
14	M/31	181/78	1	2	9	0000	1000	2–11	2111	1121	0011	2121	101	C A3	I
15	M/35	173/78	2	3	60	20–0	22–1	32––	3232	3332	2221	3332	100	C A6	U

A Case
B Sex/age
C Height/weight
D Appearance
  1 sudden
  2 gradually
  3 trauma
E Activity
  1 competition
  2 training
  3 recreational motion
  4 other
F Duration of symptoms, months
G–M Symptoms at 0, 6, 10, and 58 weeks
  0 no
  1 slight
  2 moderate
  3 severe
G Pain on palpation
H Pain on pressing patella against femur
I Pain during apprehension test
J Pain going downstairs
K Pain when squatting
L Hindrance to normal life
M Hindrance to sports activities
N Overall therapautic effect at 6, 10, and 58 weeks
  0 no
  1 slight
  2 moderate
  3 good
O Patellar damage at the beginning of the trial
  Localization
    M medial
    C central
    L lateral
  Type
    A fissure
    B fibrillation
    C undulation
  Size (cm^2)
P Change in the macroscopic damage of the patellar cartilage
  W worse
  U unchanged
  I improved

During the trial, 2 patients were excluded according to the protocol: 1 had acute trauma to the knee after 6 injections, and 1 dropped out after 8 injections. Thus, 14 patients in the GAGPS group and 15 patients in the placebo group remained for final analysis (Table 1).

Each patient was always examined by the same physician (TR or KV) on entry (Week 0), before the last injection (Week 6), and after the 1-month (Week 10) and 1-year (Week 58) follow-up periods. Control arthroscopy was performed at the 1-year follow-up. The initial and control arthroscopies were all performed and evaluated by TR.

The following parameters were recorded in the clinical evaluation: pain on palpation, pain when pressing the patella against the femur, pain during the apprehension test (tightening of the quadriceps muscle with the leg stretched while the physician

prevents the patella from moving upwards), pain when going downstairs, pain during squatting, hindrance to normal life and sports activities. All of these parameters were evaluated using a four-point scale. Occurrence of hydrops, locking, giving way, and crepitation were also recorded. The physician's evaluation of the overall therapeutic effect was assessed using a four-point scale.

Macroscopic damage of the patellar cartilage (fissures, fibrillations, fragmentation, softening, and the size of the lesion) was recorded at both arthroscopies (Table 1). Changes of the damage (worse, unchanged, improved) were based on comparing the findings in the initial arthroscopy and the 1-year follow-up arthroscopies. The comparison was done blindly from verbal arthroscopy records before breaking the code.

The occurrence of side effects was established before repeat injection using a simple nonleading question, and this information was recorded on the case report form. One patient in the GAGPS group reported sweating and dizziness after the 4th injection. However, the treatment was not discontinued, and the symptoms did not reappear after the subsequent injections.

Rearthroscopy at the 1-year follow-up could be done on 26 patients. One patient in the GAGPS group was lost to follow-up at the final evaluation, and 2 patients in the placebo group refused rearthroscopy (1 of them was asymptomatic, and the other had moderate to severe clinical symptoms).

Comparison of baseline characteristics and the statistical analysis on comparing the two treatment groups at the different assessment times were done with the Wilcoxon test. The 95 percent confidence limits were calculated according to Pocock (1983). All *P*-values are based on two-sided tests. A single overall test of the null hypothesis of no treatment effect, taking all parameters into account, was performed applying the method proposed by O'Brien (1984), thus keeping the overall Type I error rate bounded by $\alpha = 5$ percent (two-sided).

Table 2. Change in the macroscopic damage of the patellar cartilage at the 1-year follow-up

	GAGPS	Placebo
Worse	0	3
Unchanged	5	7
Improved	8	3

$P = 0.026$.

Hydrops, locking, and giving way were recorded only in a few patients in both groups, and were thus useless as parameters. Crepitation was present in 10 patients in the GAGPS group and in 13 patients in the placebo group on entry to the study. The corresponding values at 1 year were 6 and 13, respectively.

The rearthroscopies revealed improvement in 8/13 in the GAGPS group compared with 3/13 in the placebo group (Table 2). In the GAGPS group the following improvements were seen: Of 5 patients with fissures at the initial arthroscopy, 2 were fully healed, 1 only showed surface undulations, and in 2 the size of the lesion was reduced. Of 3 patients with fibrillations, 1 was fully healed and 2 showed surface undulations. In the placebo group, 2 patients with fissures showed reduction in size of the lesion, and 1 patient with fibrillations was fully healed.

All the parameters except "pain on palpation" showed the same general outcome with reduction in severity of the symptoms at 1 month followed by further reduction in the GAGPS group, while in the placebo group there was an increase in severity (Figure 1).

The overall test for the multiple endpoints revealed a substantial difference ($P = 0.011$) between the two treatment groups. The same was also revealed by the physician's evaluation of the overall therapeutic effect at 1 year, as a clear improvement was recorded in 10/14 of the GAGPS-treated patients as compared with 3/15 of the placebo-treated patients.

Results

At the final 1-year evaluation, all the clinical parameters but "pain on palpation," "pain on pressing," and "hindrance to sports activities" showed a difference between the treatment groups. This difference was not seen directly after the injection period.

Discussion

In several experimental studies, GAGPS has been shown to have a protective effect on damaged cartilage by inhibiting catabolic enzymes (Howell et al. 1986, Altman et al. 1987, Halverson et al. 1987, Andrews et al. 1985, Carreno et al. 1986, Hannan et al.

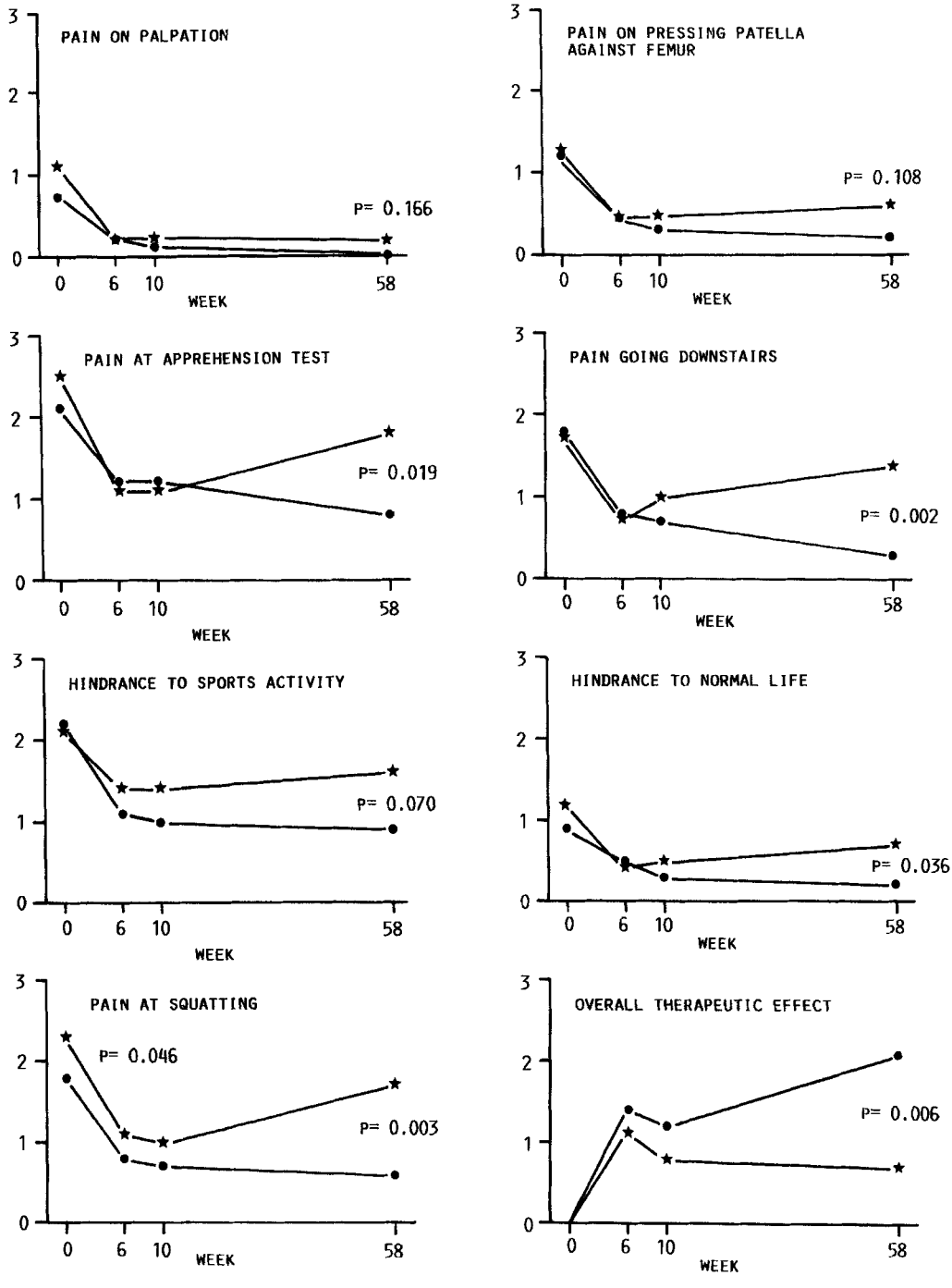

Figure 1. The clinical parameters expressed as mean values. 0 none, 1 slight, 2 moderate, 3 severe. In overall therapeutic effect, 3 good. ● GAGPS, ★ Placebo. *P*-values by two-sided Wilcoxon test.

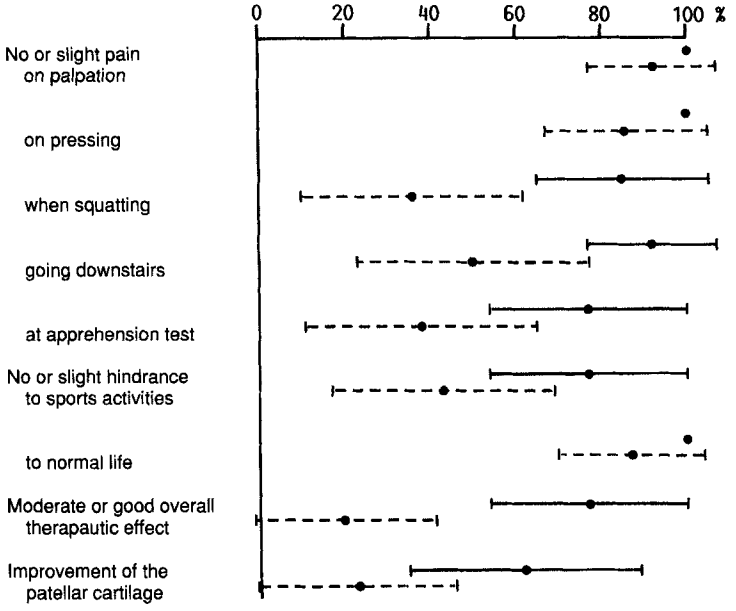

Figure 2. The 95 percent confidence limits for the relative number of patients with a clinically good result at the 1-year follow-up. —— GAGPS, - - - - placebo.

1987) and by stimulating the metabolism of chondrocytes and synovial cells (Hannan et al. 1987, Dustman et al. 1974, Olijhoek et al. 1988).

The results of our arthroscopies indicate that GAGPS had a healing effect on damaged patellar cartilage. The results of the clinical parameters correlated well with the result of the arthroscopies. Patient assessment of hindrance to sports was an unsuitable parameter because our patients discontinued sports activities at least temporarily during the study. Patient assessment of hindrance to normal life describes the overall hindrance to the usual activity the patient was accustomed to.

The effect of quadriceps training and the interruption of sports activities in combination with a possible placebo effect of the injections may explain the good results at the 1-month follow-up. The healing processes within the cartilage seem to exert a long-term effect as judged by the good results the clinical parameters showed at the 1-year follow-up (Figure 2). Our results were of the same magnitude as reported in earlier studies on GAGPS in chondromalacia of the patella (Paul and Franke 1974, Malze 1983).

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