Double-blind, randomised, placebo controlled, multi-centre study verifying the effect of Geladrink Forte preparations in patients with knee osteoarthritis.

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Introduction:
Osteoarthritis (OA) is a disorder of the synovial joints, which is characterised by a loss of joint cartilage, subchondral bone remodelling, formation of osteophytes and inflammation of the synovial membrane (1). It is the most common joint disease, which affects up to 12% of the population (2). Causal therapy for OA is not currently available and therefore therapy for OA focuses on the relief or removal of pain, maintenance of function and potentially also on slowing or stopping its radiological progression.

The European League Against Rheumatism (EULAR) has published guidelines for the treatment of knee (3) and hip (4) osteoarthritis. It emphasizes several general principles, which include education of the patient, an individual therapeutic plan for each patient and a combination of pharmacological and non-pharmacological therapy. The drug of first choice in the treatment of pain is still recommended to be paracetamol due to its safety and price. Nevertheless its analgesic efficiency is often insufficient in OA and it is necessary to use non-steroid anti-inflammatory drugs (NSAIDs). These drugs have a wide range of adverse effects however, especially gastrointestinal effects (5). Selective COX-2 inhibitors have a better GIT safety profile, but the issue of thrombotic, cardiovascular and renovascular adverse effects remains unresolved. The latest papers indicate that it is present in all NSAIDs, and not only in COX-2 selective (7, 8). EMEA therefore recommends using NSADs in the lowest dose possible for the shortest time possible.

The group of SYSADOA (Symptomatic Slow Activity Drugs in OA) includes glucosamine (GS), chondroitin sulphate (CS), hyaluronic acid and diacerhein. The mechanism of their action is not the direct influence of inflammation via the cyclo-oxygenase pathway and production of prostaglandins, but another effect directly on the cartilage metabolism (chondrocytes) or metabolism of the synovial membrane (synoviocytes). In many cases the direct mechanism of action is unknown, however. Typical for the whole group is the kinetics of the effect – slow onset of the effect, but persistence of the effect after the withdrawal of therapy. Due to the possible action mechanism, SYSADOA are great candidates for structure modifying drugs. Some studies with glucosamine (9, 10) and chondroitin sulphate (11) have also confirmed this effect.

Although the recommendations of EULAR, prepared according to the principles of evidence-based medicine, recommend SYSADOA drugs, e.g. ACR, it is markedly reserved with the exception of hyaluronic acid. In the interests of objectivity, it should be stated that there are also negative studies dealing with GS and CS (11). Even the great independent study sponsored by NIH GAIT has not proved the efficiency of GS and CS, even in combination. However, in predefined groups of patients with greater pain, the combination of GS and CS is more effective than a placebo and even more effective than NSAIDs (celebrex) (12).

Geladrink is a composite preparation containing 3300 mg of collagenous hydrolysate (Gelita), 1500 mg of GS, 800 mg of CS and other substances (natural MSM 600 mg, vitamin C 100 mg, vitamin E 50 mg, selenium 50 μg, manganese 2.0 mg and extract of Boswellia Serrata 100 mg). It is an over-the-counter preparation, distributed as a dietary supplement.

Nevertheless we decided to perform a rigorous randomised controlled study to verify the efficiency of this promising combination.

Goals:

The primary goal of this study was to confirm the statistically significant difference of the multi-component preparation Geladrink Forte (the main components in a daily dose include: collagenous peptides GELITA® 3300 mg, glucosamine sulphate 1500 mg, chondroitin sulphate 800 mg) compared to a placebo based on an evaluation of pain during walking (20 m) on a VAS according to Huskisson in the time of visit T0 (prior to the initiation of therapy) and in T2 (i.e. in the 90^{th} day of therapy – after the termination of therapy).

The secondary goals were as follows:

- To compare the efficiency of therapy the same way as in the primary goal for the tested preparation and active comparator, which was collagenous hydrolysate in a daily dose of 10 g.
- The comparison of function of observed joints affected with OA (evaluated using the Lequesne algo-functional index) between the treated groups.
- Comparison of changes of biochemical parameters (ultra-sensitive CRP, chondrex, urine pyridinoline and deoxypyridinoline) from baseline (T0) between treated groups.
- Comparison of patient and physician evaluations of therapy after the end of therapy (T2) between the treated groups.
- Evaluation of pain in other joints using VAS.
- Evaluation of the carry-over effect 30 days after the termination of therapy (T3).
- Use of paracetamol during the study.

Methods:

Inclusion criteria:

- Femoro-tibial knee osteoarthritis II and III stages diagnosed and classified in accordance with the Kellgren-Lawrence criteria.
- Clinical symptoms of OA persisting during the last three months.
- Pain during walking on the Huskinsson scale (VAS) $\geq$ 40 mm (pain in the course of daily activities).
- Lequesne Index $\geq$ 8 points
- Age 50-75 years

Exclusion criteria:

- Isolated patello-femoral OA (or predominant).
- Femoro-tibial knee osteoarthritis I and IV stage diagnosed and classified in accordance with the Kellgren-Lawrence criteria.
- Genu varum or valgum > 8^{o}
- Surgical procedure on the knee in the six months before the beginning of the study.
- Secondary osteoarthritis (arthritis, metabolic arthropathy, Paget's disease).
- SYSADOA used in the last three months.
- Intra-articular administration of steroids in the course of the last month.
- Use of any corticoid in the course of the last 3 months (intranasal and inhalation corticoids for the therapy of asthma and sinusitis was approved).

Study design

The study was a multi-centre, parallel, randomised and double-blind study. One hundred fifty patients were randomised in five centres (rheumatology workplaces) in the Czech Republic and the division of each therapeutic group was in a ratio of 1:1:1 (Geladrink Forte : Collagenous hydrolysate : Placebo). The patients were randomised in one of the 3 branches: 1. Geladrink Forte (collagenous peptides 3300 mg, glucosamine sulphate 1500 mg, chondroitin sulphate 800 mg), 2. collagenous peptides 10 g, 3. placebo. Paracetamol was used as emergency medication in a maximum dose of 2g/day. The wash-out period for NSAIDs took place prior to the actual medication, which depended on the type of medicine, which had been administered so far and was at least 5 elimination half-lives of the medicine used. Double-blind therapy took place for 90 days (T2) with a follow up after the 45^{th} day (T1) and a subsequent 30-day observation and evaluation of the persistence of the therapeutic effect was performed (carry-over effect – T3).

The efficiency of the medication was primarily measured on the basis of the evaluation of pain during walking (20 m on a flat surface) on the VAS according to Huskinsson. Secondary parameters included comparison of the function of the observed joint affected with osteoarthritis (evaluated with Lequesne algo-functional index), evaluation of the carry-over effect 30 days after the termination of therapy (T3) and the consumption of paracetamol during the study. The goal of the comparison of changes of biochemical parameters (ultra-sensitive CRP, chondrex, urine pyridinoline and deoxypyridinoline) from the baseline (T0) between the treated groups was to objectify the evaluation of the effect of individual medications. Adverse effects and events were observed, but since the substances used in the study did not have very good tolerance in the previous studies, statistical evaluation was not performed.

A population according to the *Intention-To-Treat* (ITT) principle was used for the primary analysis. Due to this, the patients were analysed regardless of any deviation from the plan, i.e. deviation from the study protocol. This principle was used because of the plan and arrangement of the study, it is a conservative procedure. The population of patients with no serious deviation from the protocol (PPS) was used for the secondary analysis, so that it was possible to demonstrate the sensitivity of the main study results to such deviations.

In accordance with the primary goal, the intensity of pain during a 20-meter walk was evaluated (VAS) in great detail. A decrease of the intensity of pain on VAS was calculated relative to the value prior to the therapy, i.e. the measured PID (*pain intensity difference*). A Wilcoxon test was performed during all visits (T1, T2, T3) for the *PID* in order to find the statistical significance of differences between the treated groups.

Results:

Significant differences for observed measures prior to the start of medication between therapeutic groups were not found (for: age, body height, weight, intensity of pain during a 20m walk – VAS, Lequesne algo-functional index, intensity of pain in other joints on VAS, evaluation by a physician and patient, concomitant therapy upon entry to the study, relevant previous therapy prior to entry to the study, biochemical parameters). The representation of patients with various stages of OA was very similar as well. There were more men in the Geladrink Forte and collagenous hydrolysate group compared to the group with the placebo (see Table No. 1). It is probably of no greater importance in the evaluation, however.

There were in total 150 patients included in the study, whereas there were 144 patients available for the statistical processing (ITT population).

The basic statistics show a certain decrease in pain intensity in the sense of increased *PID* on T1 (45 days), which is greater for Geladrink Forte and collagenous hydrolysate compared to the placebo. It is not, however statistical significance on the significance level of $\alpha = 0.05$. The differences of active therapeutic groups from the placebo are for T2 (90 days) here, in comparison with visit T1 expressed more and for the Geladrink Forte/placebo difference they reach a statistical significance on the significance level of $\alpha = 0.05$, where the p-value is 0.0427 (see Chart No.1). The population of patients without a greater deviation from the protocol (PPS, number of subjects = 123) in T2 was used for secondary analyses. The average values of PID for Geladrink Forte (32 mm) and collagenous hydrolysate (29 mm) were higher compared to the placebo (20 mm) (see Chart No. 2). The difference between Geladrink Forte and the placebo as well as the difference between collagenous hydrolysate and the placebo are statistically significant on the significance level of $\alpha = 0.05$ for this selected group of patients. The evaluation of persistence of the therapeutic effect after 30 days of the termination of medication (T3) provided no statistically significant differences between the groups.

The intensity of pain in other joints (on VAS) decreased during the administration of medication, it was borderline for collagenous hydrolysate, nevertheless differences between the therapeutic groups are not statistically significant in the significance level of $\alpha = 0.05$.

The Lequesne algo-functional index decreased during the study in all study groups. The differences between individual groups were not statistically significant.

The majority of the patients reported an improvement in the evaluation by a physician, as well as in their own evaluation. Improvement in the group Geladrink Forte was slightly more in both cases than in the other groups (68.8% for Geladrink Forte compared to 58.3% for the placebo), from the statistical point, these differences are not significant (Table No. 2).

The study subjects were allowed to use paracetamol as a co-administered medicine (emergency medication). The patients were using paracetamol in a relatively low extent. Nevertheless the number of paracetamol tablets (1 tbl. = 500 mg) was lower in Geladrink Forte than in the placebo (18 compared to 31 in the T0-T1 period and 22 compared to 37 in the T1-T2 period). This means a reduction of emergency medication by 40% in each period of observation (see Table No. 3).

During visit T0 and visit T2 (prior to and after the withdrawal of medication) samples were collected for the determination of urine pyridinoline, deoxypyridinoline, chondrex and ultra-sensitive CRP in order to objectify the conclusions of this study. There are no obvious changes in the CRP and chondrex in relation to the therapy or any differences between therapeutic groups.

The levels of pyridinoline and deoxypyridinoline for each therapeutic group are provided in Chart No. 3. In pyridinoline a decline of the levels after therapy is obvious in all groups. It was lowest in the placebo, in average (-3.4 nmol/mmol). A statistically significant decrease was observed in Geladrink Forte compared to the placebo (average decline = - 7.0

nmol/mmol) with a significance level of $\alpha = 0.05$ with p-value = 0.036. Collagenous hydrolysate had on average a similar decline as Geladrink Forte (-7.3 nmol/mmol), but a statistical significance compared to the placebo was not proved (the levels of pyridinoline in collagenous hydrolysate have shown greater variance). A very similar situation was seen in deoxypyridinoline. Patients who received Geladrink Forte showed a statistically significant decline in the level of deoxypyridinole (on average by -1.5 nmol/mmol) compared to the placebo (-0.6 nmol/mmol) on a significance level of $\alpha = 0.05$, where p-value = 0.0174 (Chart No. 4)

Discussion:

The pharmacotherapy of pain in OA is still based on weak and strong analgesics, non-steroidal anti-inflammatory drugs (NSAIDs) and coxibes. More than half of the patients then usde NSAIDs for a long time despite the risk of patients with symptomatic OA (age, polymorbidity, polypragmasia) being several times higher than in other indications.

Drugs from the SYSADOA group could represent an appropriate means to treat OA. Besides the symptomatic effect on pain and function, they have a positive effect on the metabolism of the cartilage and a potential effect to slow the radiological progress (9, 10). The most discussed preparation in the past years from the entire group was glucosamine (13). It is, however necessary to differentiate glucosamine sulphate from glucosamine hydrochloride during the evaluation of glucosamine. The development of new technologies enabled better pharmacokinetic studies, which show up to three times greater biological availability of glucosamine sulphate than glucosamine hydrochloride (14). The role of sulphate groups in the effect on the metabolism of chondrocytes (15) has been discussed as well. The action mechanism was newly suggested as well, based on in vitro studies. Glucosamine inhibits IL-1 induced gene expression, which is an inhibition of NF kappa B on the level of chondrocytes and synoviocytes (16), which results in the simultaneous decrease of COX-2 synthesis, PGE_2, NO and IL-1 induced synthesis of metaloproteinases (16).

The evidence of clinical effects of glucosamine is controversial. The issues of almost all pharmaceuticals with analgesic effects in OA are reflected there: heterogeneity of the disease, different mechanism of the origin of pain, variations of activity, measurement of pain as a subjective parameter, great placebo effect, necessity to administer emergency medication, ethical issues of long-term studies, complexity of morphological evaluation of OA progression (17). It is nevertheless necessary to state that if evidence-based medicine principles were used, the evaluation of GS was positive and the preparation was recommended (first and second Cochran analysis [18]), Recommendations of EULAR for the therapy of the knee joints OA (3).

The loss of chondroitin sulphate from the cartilage is a part of the ageing process in osteoarthritis. This fact is a practical basis for the administration of exogenous CS. It seems that exogenous CS is partially absorbed in the form of a high molecular polysaccharide together with the derivates from partial de-polymerisation and desulphatation (19). The symptomatic efficiency of CS was confirmed in a meta-analysis by B. Leeb (20) and T. McAllindon (21) as well as in the Recommendations of EULAR for the therapy of the knee joints OA (3). Two independent randomised studies have also shown a slowing effect of CS on the progress of OA (11, 22). The newly completed study STOPP (23) has also shown a structure-modifying effect of CS.

Glucosamine and chondroitin sulphate were tested mostly in monotherapy. The first up-to-date quality study, which evaluated the combination of GS + CS compared to a placebo, a monotherapy of GS and CS and compared with the active comparator (celebrex) was the GAIT study. Analysis of the primary parameter has shown no effect of the combination of GS + CS compared to a placebo, nevertheless this combination was relatively highly effective in cohorts of patients with greater pain (12). The results of our new study confirm the potential of the GS + CS combination.

The issues of using collagenous hydrolysate in OA have been discussed in detailed articles by Moskowitz (23) and Bello (24). 4 open and 3 double-blind studies (25) have been identified. Since the quality of studies was not always optimal, it seems that there is more evidence of a possible effect of this therapy. Further studies are, however necessary.

Conclusion

The performed double-blind randomised controlled study has shown a symptomatic efficiency of the Geladrink Forte composite nutrition preparation on pain compared to a placebo. The difference between the tested preparation and a placebo is approximately 10.0 mm, which corresponds to the extent of the effect in studies with non-steroidal anti-inflammatory drugs. No difference in the effect on the function was found in this study, however. An approximately 40% lower consumption of additional analgesics was, however observed. Practically no adverse effects were observed afterwards during the therapy.

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Table No. 1:

	GELADRINK FORTE	KOLAGENNÍ HYDROLYZÁT	PLACEBO	CELKEM
	N = 48	N = 48	N = 48	N = 144
Demografické veličiny				
Věk v letech (SD)	65 (7)	63 (8)	66 (7)	65 (7)
Pohlaví (%)				
Muž	13 (27.1%)	13 (27.1%)	6 (12.5%)	32 (22.2%)
Žena	35 (72.9%)	35 (72.9%)	42 (87.5%)	112 (77.8%)
Faktory související s onemocněním léčeným ve studii				
Klasifikace podle Kellgrena-Lawrence				
Stupeň II.	29 (60.4%)	25 (52.1%)	32 (66.7%)	86 (59.7%)
Stupeň III.	19 (39.6%)	23 (47.9%)	16 (33.3%)	58 (40.3%)
Lequesne algofunkční index (SD)	12.0 (2.0)	11.9 (2.5)	12.4 (2.4)	12.1 (2.3)
Trvání onemocnění v letech (SD)	8.2 (8.7)	6.3 (6.1)	6.3 (6.7)	7.0 (7.3)
Bolest při chůzi v mm VAS (SD)	60.5 (11.5)	60.4 (11.8)	62.2 (13.9)	61.1 (12.4)
Ostatní klouby, bolest v mm VAS (SD)	46.8 (17.2)	44.8 (19.8)	45.8 (20.6)	45.8 (19.1)
Další faktory, které mohou ovlivnit účinek léčby				
Výška v cm (SD)	169 (9)	167 (8)	164 (8)	167 (8)
Hmotnost v kg (SD)	83 (12)	84 (13)	79 (12)	82 (12)

	GELADRINK FORTE	COLLAGENOUS HYDROLYSATE	PLACEBO	TOTAL
	N = 48	N = 48	N = 48	N = 144
Demographic parameters				
Age in years (SD)	65 (7)	63 (8)	66 (7)	65 (7)
Gender (%)				
Man	13 (27.1%)	13 (27.1%)	6 (12.5%)	32 (22.2%)
Woman	35 (72.9%)	35 (72.9%)	42 (87.5%)	112 (77.8%)
Factors related to the disease treated in the study				
Classification according to Kellgren-Lawrence				
Degree II	29 (60.4%)	25 (52.1%)	32 (66.7%)	86 (59.7%)
Degree III	19 (39.6%)	23 (47.9%)	16 (33.3%)	58 (40.3%)
Lequesne algo-functional index (SD)	12.0 (2.0)	11.9 (2.5)	12.4 (2.4)	12.1 (2.3)
Duration of the disease in years (SD)	8.2 (8.7)	6.3 (6.1)	6.3 (6.7)	7.0 (7.3)
Pain during walking in mm VAS (SD)	60.5 (11.5)	60.4 (11.8)	62.2 (13.9)	61.1 (12.4)
Other joints, pain in mm VAS (SD)	46.8 (17.2)	44.8 (19.8)	45.8 (20.6)	45.8 (19.1)
Other factors, which may influence the effect of therapy				
Height in cm (SD)	169 (9)	167 (8)	164 (8)	167 (8)
Weight in kg (SD)	83 (12)	84 (13)	79 (12)	82 (12)

Table No. 2:

a) Summary of changes in the physician's evaluation in visit T2 compared to visit T0 (ITT)

	GELADRINK FORTE	COLLAGENOUS HYDROLYSATE	PLACEBO
Improvement	31 (64.6%)	28 (58.3%)	28 (58.3%)
No change	15 (31.3%)	16 (33.3%)	17 (35.4%)
Worsening	2 (4.2%)	4 (8.3%)	3 (6.3%)
Total	48 (100%)	48 (100%)	48 (100%)

b) Patients with an improvement in physician's evaluation: differences between treatment groups (ITT)

	p-value	95% IS		
GELADRINK FORTE - PLACEBO	0.6749	-15.3%	-	27.8%
GELADRINK FORTE – COLLAGENOUS HYDROLYSATE	0.6749	-15.3%	-	27.8%
COLLAGENOUS HYDROLYSATE - PLACEBO	1.0000	-19.7%	-	19.7%

c) Summary of changes in the patient's evaluation in visit T2 compared to visit T0 (ITT)

	GELADRINK FORTE	COLLAGENOUS HYDROLYSATE	PLACEBO
Improvement	33 (68.8%)	30 (62.5%)	28 (58.3%)
No change	10 (20.8%)	14 (29.2%)	15 (31.3%)
Worsening	5 (10.4%)	4 (8.3%)	5 (10.4%)
Total	48 (100%)	48 (100%)	48 (100%)

d) Patients with an improvement in patient's evaluation: differences between treatment groups (ITT)

	p-value	95% IS		
GELADRINK FORTE - PLACEBO	0.3963	-10.8%	-	31.6%
GELADRINK FORTE – COLLAGENOUS HYDROLYSATE	0.6674	-14.8%	-	27.3%
COLLAGENOUS HYDROLYSATE - PLACEBO	0.8347	-17.5%	-	25.8%

Table No. 3:

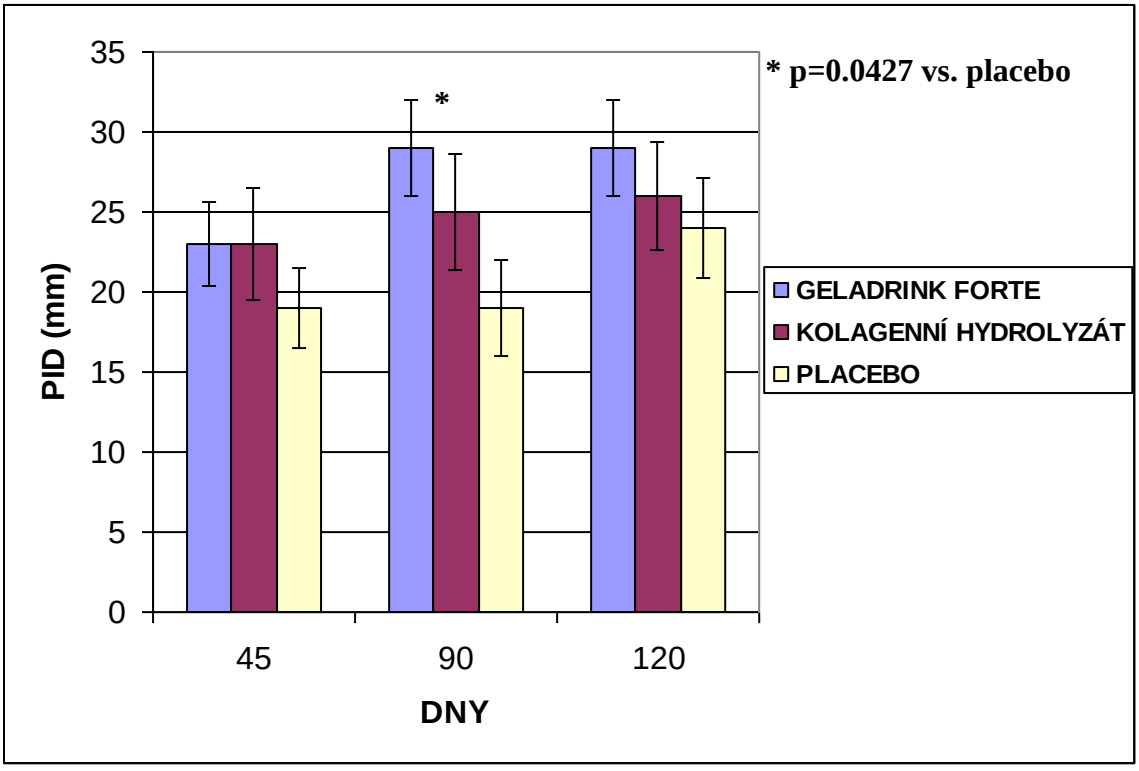
Consumption of paracetamol (in number of paracetamol tablets during the period of observation) expressed by the median value (ITT).

	GELADRINK FORTE	KOLAGENNÍ HYDROLYZÁT	PLACEBO
	medián	medián	medián
T0 - T1 (tbl)	18	23	31
T1 - T2 (tbl)	22	25	37

COLLAGENOUS HYDROLYSATE

median median median

Chart No. 1: PID (in mm) for controls in T1, T2 and T3 (45, 90, 120 days) (ITT)



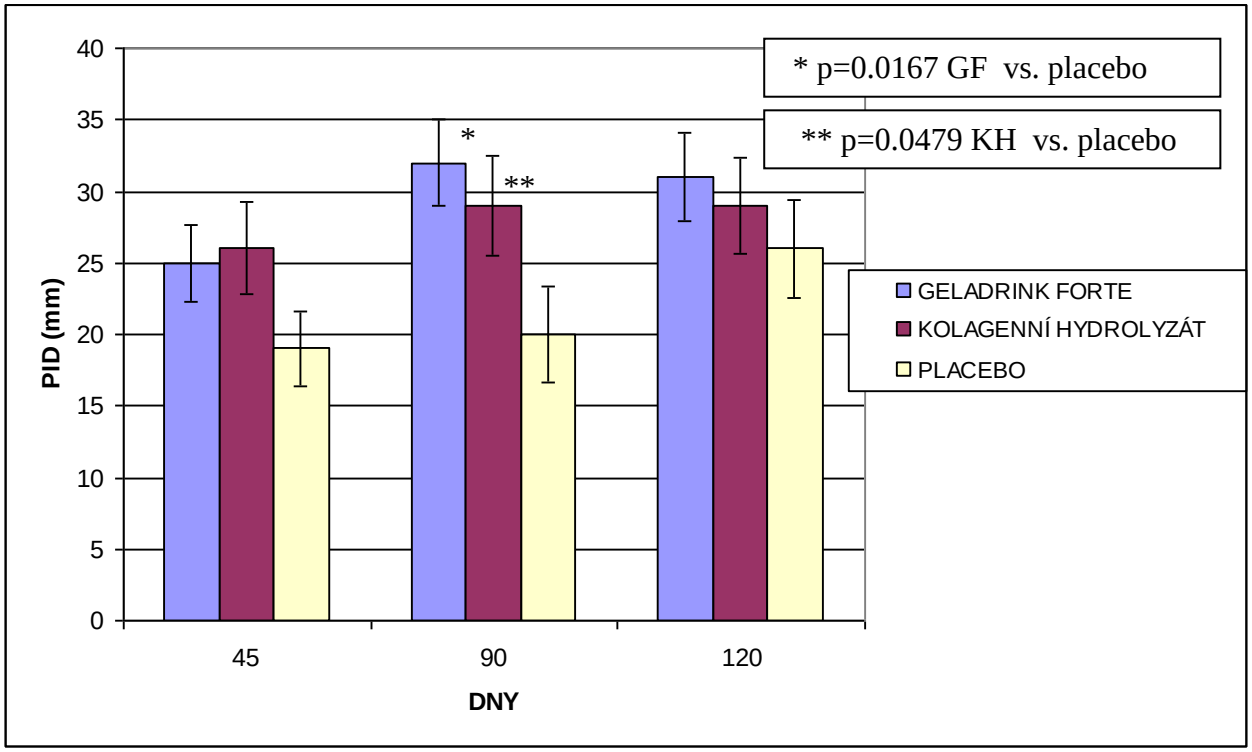
against placebo

COLLAGENOUS HYDROLYSATE

DAYS

Note: standard deviations (SD) from the average PID value are indicated by vertical lines

Chart No. 2 PID (in mm) for controls in T1, T2 and T3 (45, 90, 120 days) (PPS)

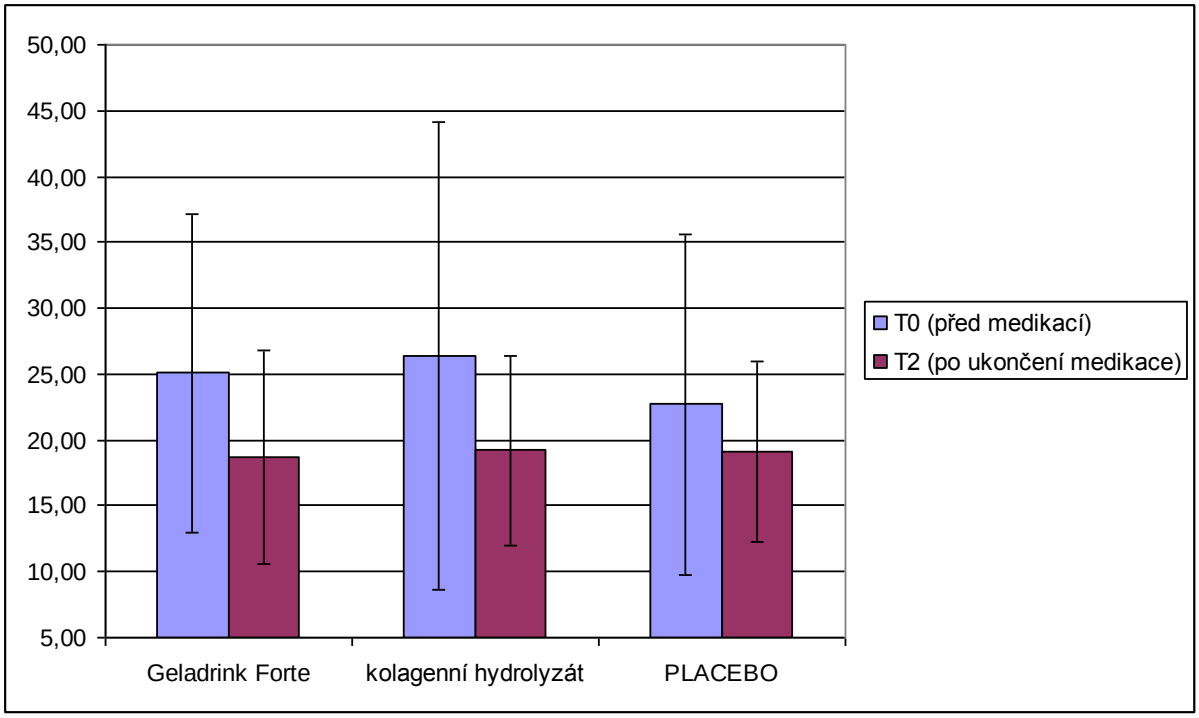


Against placebo
Against placebo
COLLAGENOUS HYDROLYSATE

DAYS

Note: standard deviations (SD) from the average PID value are indicated by vertical lines
osteoarthritis. N. Eng. J. Med. 2006;354:2184-2185.

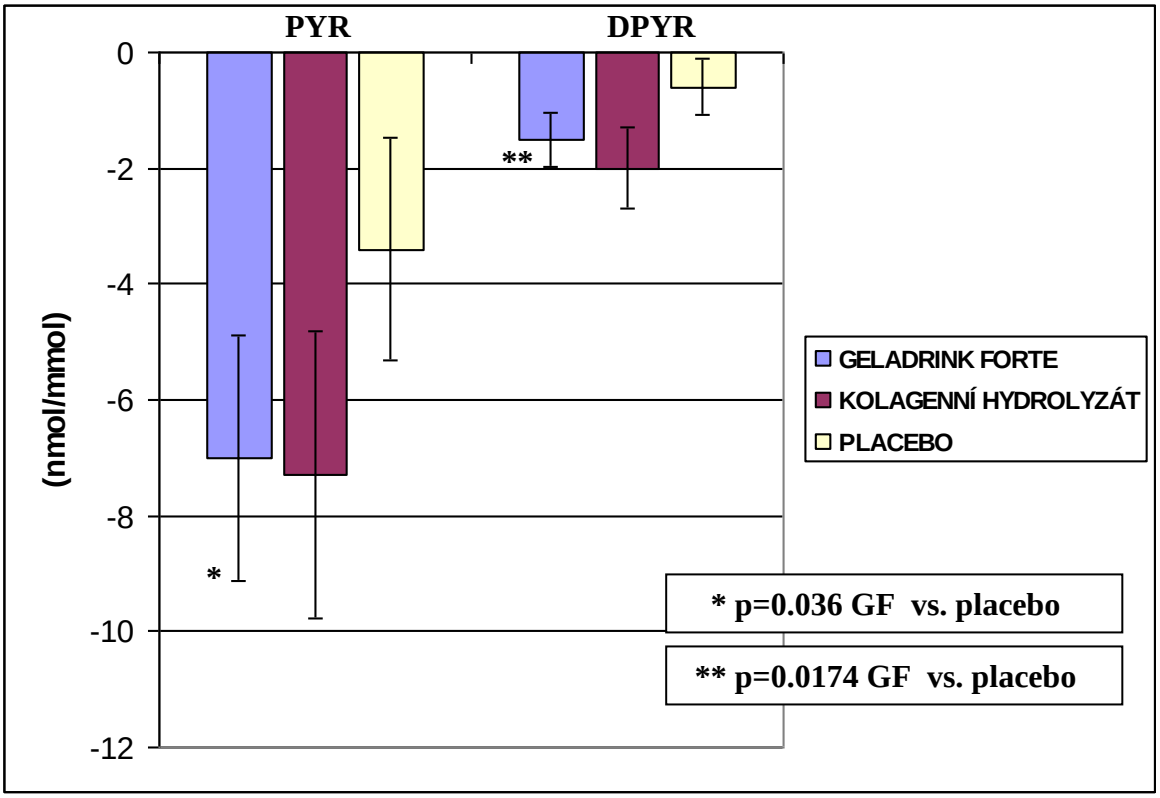
Chart No. 3:
a) Levels of pyridinoline (nmol/mmol) for individual treatment groups prior to and after the termination of medication - ITT



Before medication
After medication

Collagenous hydrolysate

Chart No. 4. Changes of pyridinoline and deoxypyridinoline in T2 compared to T0 (nmol/mmol) - ITT



Collagenous hydrolysate
Against placebo
Against placebo

Note: standard deviations (SD) from the average Pyr and DPyr value are indicated by vertical lines

Abstract

Goal of the study:
Combine the efficiency of Geladrink Forte (glucosamine sulphate 1500 mg, chondroitin sulphate 800 mg, collagenous hydrolysate 3300 mg and other substances: MSM, vitamin C, vitamin E, Se, Mn) compared to a placebo in painful knee osteoarthritis.

Methods:
Randomised controlled study in a length of 3 months plus 1 month of observation. Three branches: a) Geladrink Forte (series daily), b) collagenous hydrolysate (3300 mg), c) placebo. Paracetamol in a dose up to 2 g daily as emergency medication. The primary parameter was a change in pain when walking on VAS between the final and original value.

Patients – painful knee osteoarthritis II – III stage, VAS > 40 mm.

Results:
A total of 144 patients were included in the study. In the beginning there were no differences between the groups concerning demographic parameters or the severity of the disease. The average duration of the disease was 8 years; the average pain was around 60 mm on VAS and Lequesne index 12. There was a significantly greater decline in the value of the basic parameters (pain intensity difference – PID) at the end in Geladrink Forte compared to a placebo (29 ± 3.0 mm compared to 19.0 ± 3.0 mm, p = 0.0427). The difference was not significant in collagenous hydrolysate compared to a placebo (25 ± 3.6 against 19.0 ± 3.0, p =

0.12) in population ITT. The difference during the evaluation of patients who completed the study compared to a placebo was significant in Geladrink Forte ($p = 0.016$) as well as in collagenous hydrolysate ($p= 0.04$). Differences in the algo-functional index were not significant. Patients on Geladrink Forte used 40% less emergency medication. There was no difference in the tolerance of treatment groups.

Conclusion:
The Geladrink Forte composite preparation is efficient in the treatment of painful knee osteoarthritis.

Key words:
Knee osteoarthritis, pain, glucosamine sulphate, chondroitin sulphate, collagenous hydrolysate.