

The clinical effectiveness of viscosupplementation in intraarticular injections of hyaluronic acid. Study with ViscoPlus® Gel 2,5%, Biomedical GmbH.

Artur Gap M.D., PhD., Orthopedic Department, Jurajska Medical Center, Czestochowa,

Department of Pediatric Traumatology and Orthopedy, Silesian Medical University, Katowice, Poland.

Ryszard Tomaszewski MD., PhD., Department of Pediatric Traumatology and Orthopedy, Silesian Medical University, Katowice, Poland.

Paulina Trybek PhD., Department of Theoretical Physics, University of Silesia in Katowice, Poland

Szymon Gap Faculty of Medicine, Medical University of Warsaw, Poland

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ABSTRACT

Intraarticular injections of hyaluronic acid (IAIHA) for viscosupplementation are well documented, safe, not expensive, but still remain a controversial method of osteoarthritis (OA) treatment. In the last decade over 400 articles were published revealing miscellaneous directions of viscosupplementation research and trying to determine the place of viscosupplementation (VS) in the management of OA. The aging of developed countries population with increasing number of OA patients challenges new technologies and treatment methods to prevent the cartilage matrix degeneration. IAIHA has demonstrated in mild to moderate arthropathic changes (Kellgren-Lawrence I-III) significant efficacy in functional and pain tests vs. placebo. Remarkable majority of European orthopedics find this method efficient for moderate OA treatment due to recommendations for optimizing the results of VS and a guideline of EUROVISCO, that indicates multidirectional recommendation to IAIHA administration. In 2016 a consensus statement on the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) counted VS to the algorithm for the management of knee osteoarthritis [1]. In practical use it enhances OA treatment and allows to reduce analgesics and NSAID's administration, delaying the need for an alloplastic surgery. In recent observation we have focused on optimizing IAIHA VS treatment to

reduce complication rate to make it safe, repetitive and easy to perform procedure based on a Viscosupplementation Administration Protocol (VSAP). This requires a skilled specialist injecting ultrasound guided techniques versus blind, in aseptic operating dressing and proper patients' selection group and VS timing.

In this study increased clinical effectiveness of ViscoPlus® Gel 2,5% IAIHA for patients with OA of the knee and hip joints compared in two assessment indexes was revealed. Results of 257 patients treated with one shot ViscoPlus® Gel 2,5% visualized no complication after compliance with the VSAP conditions and clinical improvement in EVA and Laquesne scales after 6 weeks from injection. It was concluded that many predictable factors evoke final VS effect with great influence of a high molecular weight of HA and its administration protocol.

INTRODUCTION

Osteoarthritis (OA) is one of the most common diseases worldwide, the chances of an affection increase significantly with age [2]. According to the American College of Rheumatology about 70% of people over the age of 70 show symptoms of osteoarthritis, where in European population affected of OA estimated prevalence is 35% among people aged 50–59 years, and 55% for people over 70 years of age, being a frequent cause of disability [3, 4, 5]

IAIHA have been available as a OA treatment in 1980' with fair record of its apply as a viscosupplementation [6,7,8,9]. After half of a century was well known, evidence-based form of OA treatment indicated by statutory Orthopedic American and European associations [10,11]. However, due to outgoing debate, in the last decade, new statistical techniques on large case studies questioned the efficiency of biological activities of VS treatment. In 2013 AAOS CPG Guideline Review announced recommendations against viscosupplementation as an ineffective method of OA treatment. It was followed by a retrospective study of meta-analysis, double-blinded, sham-controlled trials [12]. It turned VS to not EBM proven treatment methods with equal results to placebo. Next year an AANA group supported by statistical team from Tuf's MS, evaluated statistical and analytic tools of the study, revealing wrong management and selection of trials what justified and supported usage of HA [13].

The focus of OA treatment is to reduce and control the pain related to synovial joints as well as to increase the everyday functioning [14]. Studies show that the effectiveness of products based on hyaluronic acid correlate highly with the concentration and molecular weight of the hyaluronates. The elasticity and capability of those molecules to maintain the functioning of the synovial joint is the key element which indicates the effectiveness of a therapy [15,16]. Some poor results may be due to inappropriate use of HA injections, poorly adapted to the patient's OA phenotype [17]. In the last majority of studies emphasize good results in pain decreasing rate, increasing joints ROM rate and quality of life VS treated patients [18,19,20,21].

Hyaluronic Acid (HA) is an hydrophiling glycosaminoglycan (GAG) macromolecule detected in all human tissues, building in joints cartilage extracellular matrix (ECM) and constantly occurring in healthy synovial joint fluid in amount of 1.50–3.60 mg/mL [22,23,24]. In the beginning HA was considered as a non-Newtonian liquid covering articular surfaces with lubricant to increase viscosity and elasticity of synovial fluid. Contemporary OA treatment with IAIHA shows multipotential prospects with intrinsic and

extrinsic influence on joints. In the cartilage HA complexes with binding proteins – hyaladherins, constitute appropriate ECM structure and function providing viscoelasticity to joint surfaces [21]. These complexes support angiogenesis, chondroprotection by antioxidant impact, hemostasis of ECM, healing proliferation of connective tissue and are immunosuppressive [25]. Historically the first generations HAs were animal derived, unhomogenic molecular weight organopreparates with potential of allergic reaction in a host, usually described as rare 1<10.000 [26,27,28]. Contemporary HA biosynthesis is based on bacterial fermentation with the participation of HAS-1 to 3 enzymes, and MW controlled by UDP-N-acetylglucosamine concentration [29]. It enables to produce homogenic, large molecules weight (MW) up to 10⁸ Da, safe and more predictable in effects for patients [30,31,32]. Depending on the size of the HA molecule, they show hygroscopic properties binding water approximately exceeding 1000 times their weight, conditioning the lubricating properties [33,34,20,20].

Many disciplines are sharing HA bioengineering achievements where are used in extraarticular applications proving the safety of therapy and have strong recommendations in many indications [35,36].

Synthetic HA biopolymers in cartilage have a half-life time 1-3 weeks, reaching 6 weeks in fourth generation cross-linked biopolymers [37,21,38]. Two enzymatic mechanisms - specific concerned with HYAL and nonspecific are responsible for HA degradation but majority estimated at around 70% is catabolized by the endothelial cells of the lymphatic vessels [39]. Thus in principle, long-acting HA is supposed to intensify lubrication of the articular surfaces, but the relationship between the size of the molecule and the metabolic effect on the cartilage in vivo has not been proven [40]. From that point IAIHA products should be classified separately as there are differences in IA-HA products that influence both efficacy and safety, that is confirmed by experts' experience [41]. Coexisting therapies of PRP, chondroitin sulfate with intra-articular injection of hyaluronic acid may be a perspective for the optimalization of therapy and secondary

prevention of exacerbations of OA [42, 43]. Some authors in comparative studies revealed no discrepancies between Corticosteroids and HA [44].

In arthropathies overreacting synovium produces HW and enlarge density of HA in great amount of inflammatory excessive fluid. Joint effusion dilutes them and activate enzymatic system of hyaluronidases and metalloproteinases, unprotecting cartilage from destruction [45]. Some authors, however, proves that patients with osteoarthritis have a synovial fluid with lower concentration and average molecular weight of

hyaluronates that can influence clinical effect of VS [46, 47].

The analyzed product ViscoPlus® Gel has shown, in the physicochemical analysis highest viscosity and elasticity rate based on HA. [48].

MATERIALS AND METHODS

257 cases of patients diagnosed as primary or secondary OA with mild and moderate changes were qualified to viscosupplementation [49, 50]. Patients with gonarthrosis 2 and 3 grade of Kellgren-Lawrence classification revealed with X ray exams were included in the study [51, 52].



Fig. 1 Kellgren-Lawrence 3 & 2 knee AO

Patients with AO 1 and 4 grades due to Eurovisco guidelines were excluded from the study [53]. All of them were meaningful symptomatic evidenced by physical examination protocol and LAQ and EVA score systems. Adequately to manufacture product indications patients with skin defect, rheumatoid AO and acute inflammation processes were excluded from study as well. At the visit of a patient performed in office with standard protocol, with

examination of a joint with clinical test notifications. Patient filled questionnaire with professional assist and recorded in database scoring in assessment LAQ and EVA indexes. The IAIHA was performed on a next visit (Pre-op) in the ambulatory operating room conditions after qualification up to 3 months before procedure. The treatment conditions were standardized according to the VSAP for all procedures tab. 1

Stage	IAIHA VSAP	Done
1	Sterile preparation of the treated area skin with Skinsept® Color (Ecolab) 2 x	✓
2	Prepare disposable surgical field with a drape with 10- 15 cm self-adhesive hole	✓
3	Sterile disposable cover for US linear probes 10-15 MHz	✓
4	The upper-lateral access to the suprapatellar recess of the knee joint (anterior access hip joint cavity)	✓
5	Aspiration of a joint excessive fluid (if needed)	✓
6	Ultrasound guided ViscoPlus® Gel 2,5% administration with 20G needle	✓
7	Sterile dressing of a puncture wound	✓

Tab 1. Stages of VSAP

ViscoPlus® Gel was administered observing the distribution into the joint cavity in ultrasound guidance (linear probe 10-15 MHz) and the patient's reaction. No pain and easy-spread injection of a gel during procedure was *sine qua non* condition of the joint viscosupplementation.

If any difficulties during injection occurred the access to the joint cavity had to be adjusted to avoid synovium and subcutaneous tissue infiltration with gel.

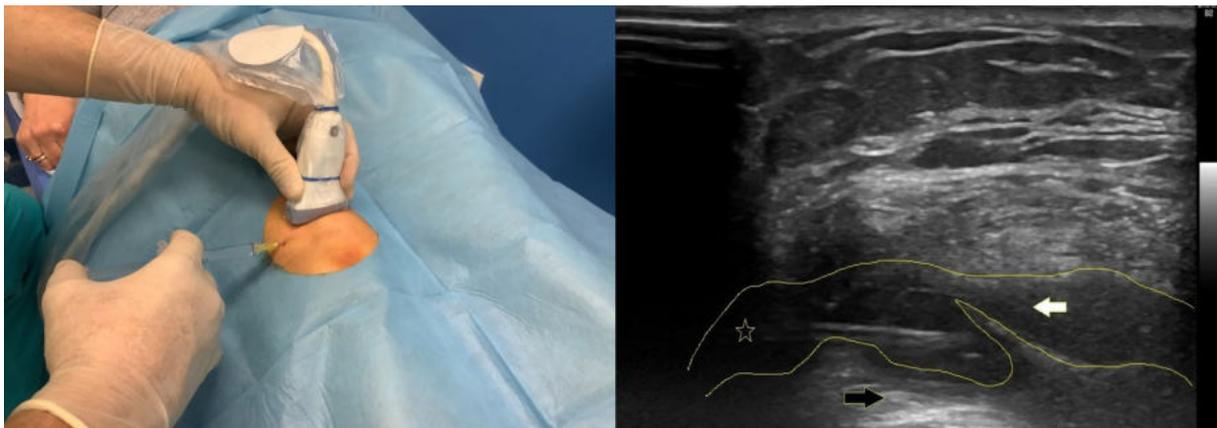


Fig 2. VSAP based injection of a knee joint. Right – ultrasound view, needle - asterix, arrow white - joint cavity infiltrated with HA, arrow black supracondylar fat pad.

Patients were given post-op indications; ice packs cooling of infiltrated site and rest for 2 days to reduce pain swelling and possible hematoma. NSAID's and pain relievers were administered only if necessary. In case of side effects patients were asked to contact operating physician. After 6 weeks on a (Post-op) visit, physical examination and whole protocol was filled due to actual clinical statement. All data were collected and digitalized to calculation sheets.

Statistical analysis was performed using Statistica version 13.1. PL, Pandas, Pingouin and Seaborn statistical packages dedicated for Python. The normality test calculated via Shapiro–Wilk formula does not allow us to confirm the

hypothesis about the normal distribution for the majority of analyzed variables at the selected significance level $\alpha=0.05$. Thus, in further analysis the non-parametric statistical tests and Spearman correlation coefficients were used in the study of statistical dependence.

RESULTS

In total 257 patients took part in the study, from eighteen orthopedic clinics in southern Poland. No pre-selection was initiated, instead the patients were selected on a purely random basis. Within the group of 257 patients, 129 were male and 128 were female. Their average age was $57,7 \pm 5,3$ years old, disease duration about 4,5

months. The average and pre-op and post-op scores were LAQ 12,5 and 6,3 points, EVA 15,9 and 9,0 points, respectively. Except one case - LAQ.

Scale pre-op ($p=0.0076$) there was no statistically significant differences between men and women due to each type of scale ($p>0.05$), tab. 2.

	N	Mean values	Median	Min.	Max.	Lower quart.	Upper quart.	Variance	STD
EVA PRE-OP	252	15,98016	15,00000	3,00000	37,00000	9,00000	21,00000	58,9757	7,67956
EVA POST-OP	252	9,06349	8,00000	0,00000	27,00000	4,00000	13,00000	38,9681	6,24244
LAQ PRE-OP	257	12,53696	13,00000	2,00000	28,00000	8,00000	15,00000	23,9137	4,89016
LAQ POST-OP	257	6,39300	5,00000	0,00000	21,00000	2,00000	9,00000	23,3801	4,83530

Tab. 2. Basic statistical values in LAQ and EVA scorings.

Many assessment scales are used to obtain most objectively patients symptoms due to specific treatment. In this paper two different evaluation methods have been chosen to avoid patient questionnaires naturally suggestibility and facilitate feedback [54]. The EVA - index as a visual-analogue scale, gives a better understanding for the relative health improvement, otherwise the Lequesne-Index gives more details about specific criteria of pain/movement source, etc. Lequesne et al developed an index of severity for osteoarthritis for the main synovial joints. This can be used to assess the effectiveness of therapeutic interventions with interpretation of scoring - each section min-max pts. 0-8, min-max pts. index score 0-24 [55]. The visual-analogue-scales EVA is a general psychometric response scale which is used in many cases, especially to describe subjective pain. The analogue aspect of the scale differentiates it from discrete scales, those analogue scales have superior metrical characteristics, thus they can be analyzed with a greater variety of statistical tools [56]. The scope of rating for the visual-analogue-scale is determined from 0 (equal to no pain at all) to 10 (very severe pain). The evaluation was performed with the help of an evaluation sheet. The multicenter evaluation protocols were analyzed according to the requirements of the two assessment scales and coexisting data. The average ratings at the pre-op visit and at the control visit pos-op were evaluated mainly based

on pain symptoms, mobility in walking and other activities, joint stiffness and overall assessment of the therapy.

In LAQ index after revealed treatment improvement from 12,5 to 6,3, that indicate according to the results decreased handicap from very severe to moderate. Following the assessment of the terms for defining the pain, we noticed that its improvement in 6 weeks after VS therapy, according to LAQ, is significant. Analysing the visual-analogue scale we have observed the decrease of the pain index from 15,9 to 9,0 that significantly reflected the improvement of the clinical condition of the treated patients. This can be understood correspondingly as a slightly-above average pain decreasing to a significantly-below average pain.

Treatment overall evaluation 2,38 pts. constituted noticed improvement effect after viscosupplementation in post-op questionnaire. Results of Wilcoxon rank non-parametric test indicate statistically significant difference between pre- and post-operative values of scales for both EVA and LAQ at the selected significance level $\alpha = 0.05$ Fig. 3. They reveal 43% decrease in EVA scoring and almost 50% in LAQ scorings. The patients covered by the study showed statistically significant improvement independently of a cohort in both scales where LAQ test as a statistical equipment more clearly emphasized statistical distribution results.

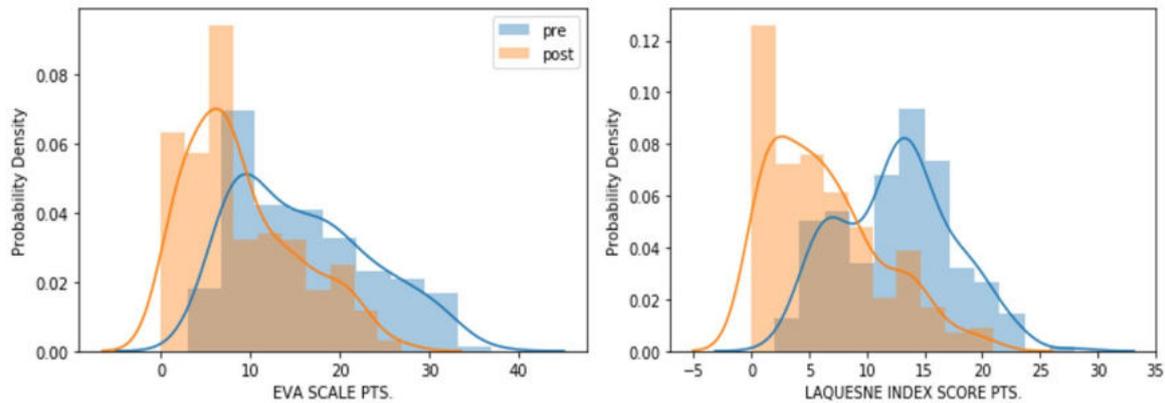


Fig 3. Probability density for LAQ and EVA scales

In the results of Mann-Whitney U test except one case - LAQ scale pre-op ($p=0.0076$) there are no statistically significant differences between men and women due to each type of the scale ($p>0.05$).

Moreover, the approximate probability distributions and the histograms already show that the LAQ scale separates pre-post patients better, compared to EVA.

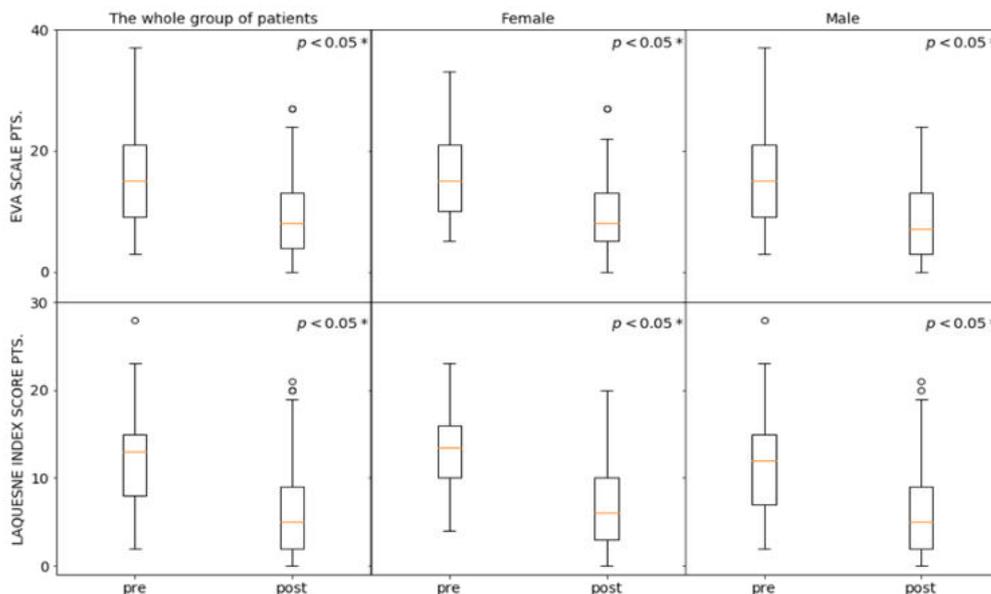


Fig. 4 Pre- and post-op results in group by sex division.

The box extends from the lower to upper quartile values. The line inside the box characterizes the median value and the whiskers represent the range of data. Outlier points are those past the end of the whiskers.

All the investigated group of age mean (male 56,0, female 59,6) indicate statistically significant differences between pre- and post-operative stage for the Wilcoxon nonparametric statistical test fig. 5.

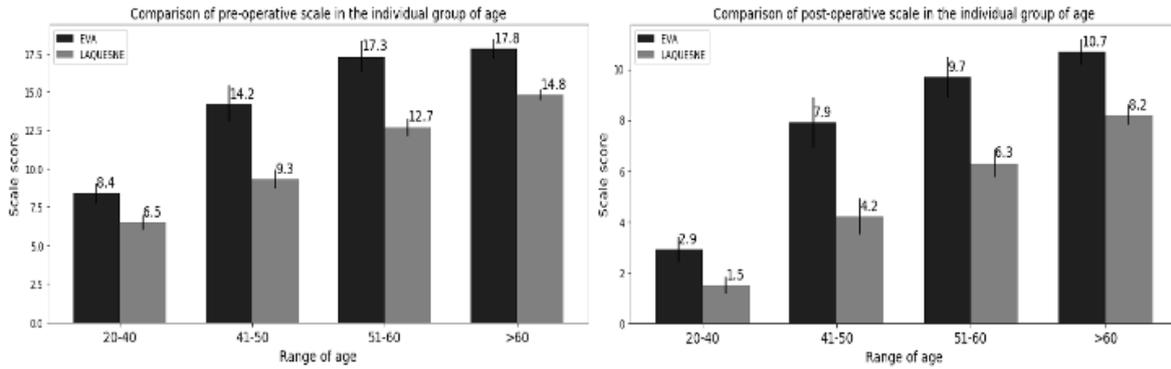


Fig. 5 Results of both scores related with age pre and post-operative

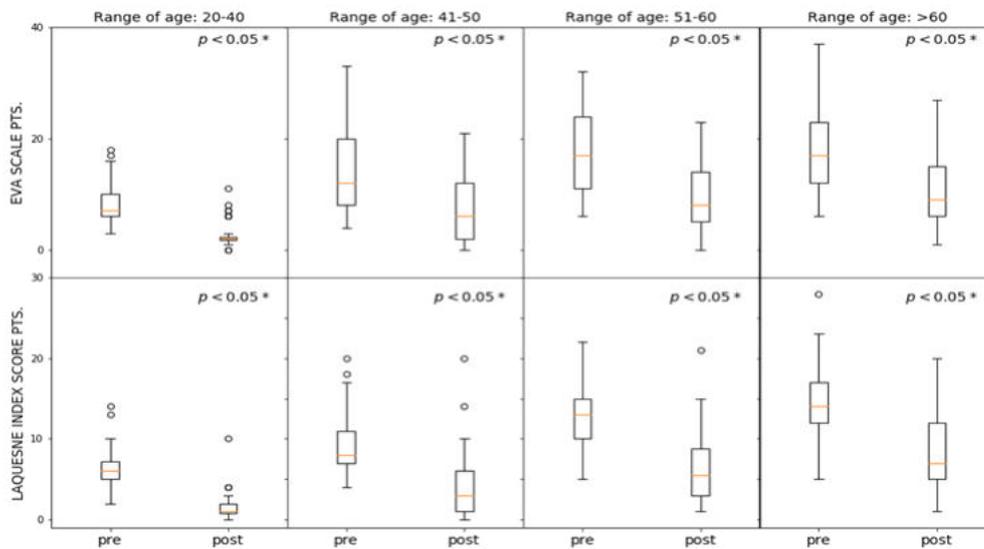


Fig. 6 Pre- and post-op EVA and LAQ scores means and standard deviation in age groups

Statistical division in age groups with use of ViscoPlus® Gel injection indicated high efficiency of the joints movement increase and the pain decrease rate, that is correlated with progressive old-aged severity of cases. Patients in fifth and sixth decade of life demonstrated high score reduction in both analyses after treatment, accordingly 6,3-7,6 for EVA and 5,1-6,4 for LAQ assessment scale. That is the target group of IAIHA treatment what is consistent with the authors' long-term observations.

It is unlikely to achieve good results for more severe cases of arthritis, but analysis revealed of ViscoPlus® Gel administration in 60+ group showed also excellent results both in EVA and LAQ (7,1-6,6). The group 20-40 years revealed very high rate average treatment effectiveness (5,5 and 6,0) but modest number of cases does not allow for unquestionable conclusions Fig. 8.

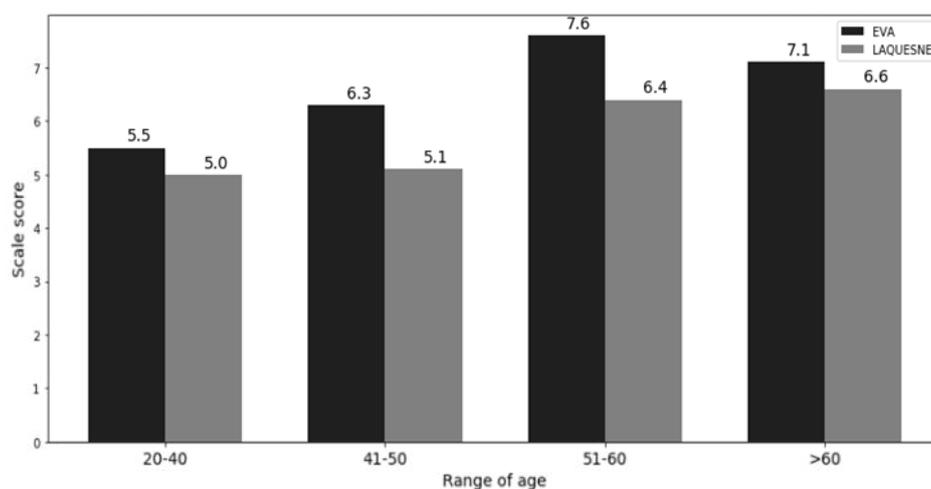


Fig. 7 Comparison of differences between pre-post mean values of scales in the individual group of age

Results of Wilcoxon rank non-parametric test indicate statistically significant difference between pre- and post-operative values in the all

investigated group of age and in score results for both EVA and LAQ, at the selected significance level $\alpha = 0.05$.

	EVA_PR E	EVA_PO ST	LAQ_PR E	LAQ_PO ST	Pain_D	AGE	POST_O P_ TREAT- MENT_E V.	VISCO- SUPLE- MENTA- TION
EVA_PRE	-	***	***	***		***	**	***
EVA_POST	0.842	-	***	***	*	***	***	***
LAQ_PRE	0.623	0.642	-	***	***	***	***	***
LAQ_POST	0.433	0.648	0.814	-	***	***	***	***
Pain Duration	0.058	0.152	0.269	0.263	-	***	***	*
AGE	0.366	0.412	0.584	0.543	0.34	-	***	***
POST-OP Treatment Eval- uation	0.172	0.379	0.375	0.556	0.217	0.253	-	***
VS result	-0.222	-0.484	-0.29	-0.502	-0.126	-0.211	-0.442	-

Tab. 3 Mutual correlations of the relevant parameters to the rating scales LAQ & EVA

Results have stronger correlation in LAQ with variables pain duration, post-op treatment evaluation, age and anticorrelated with VS results that evidence improvement of the clinical condition in both indexes whereas LAQ is more adequate.

156 patients received adjuvant therapy during treatment, mainly NSAID, which was 60.7%, what suggest high severity of symptoms and the pre -

op degree of pain. Individually, we noticed statistically significant differences in the group, confirmed by the Wilcoxon test. Comparing the groups with and without treatment values scales. Mean improvement value in a group with concomitant therapy was LAQ 6,36; EVA 7,28 and for no concomitant therapy relatively 5,81 and 6,37.

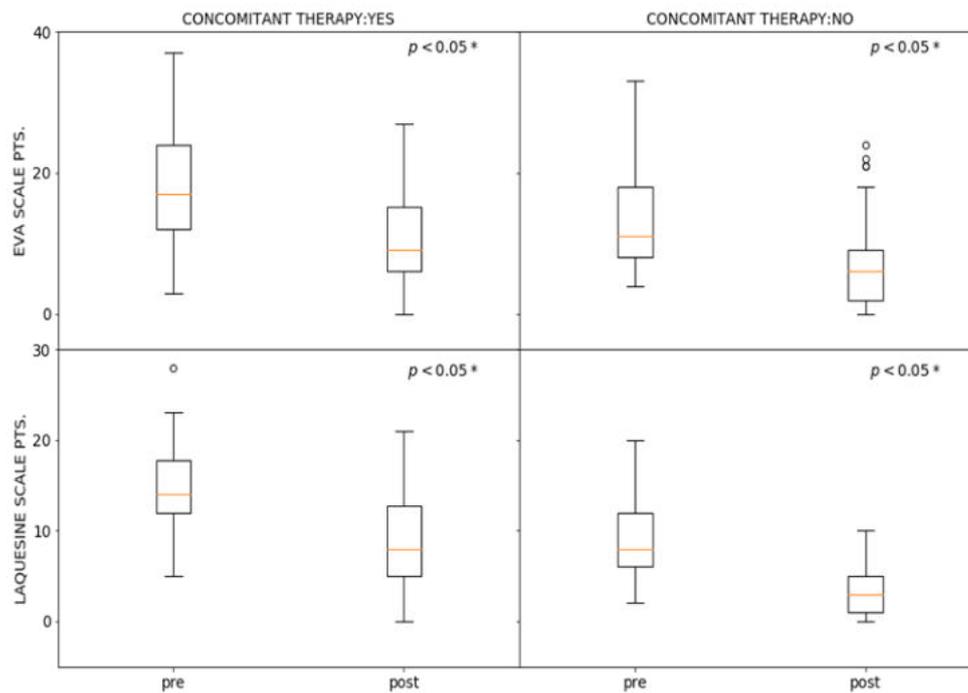


Fig. 9 Concomitant therapy significant differences in LAQ & EVA pre- and post-op

For each of the pre-post variables, Mann U Whitney test confirm the better results in the group where the adjuvant or combination therapy was administered during the 6-week follow-up period after injection.

Overall rate of adverse reactions constituted 1,9% and had a mild course of treatment and required no surgical intervention. In 5 cases, local redness, limited motion and stiffness of the joint, painful palpation of the injection site were confirmed. Concomitant, symptoms in 2 cases were acute swelling and pain in the knee, Patients reported the problem by phone and establish a check-up, usually 72 hours after the injection. In all cases ultrasound examination did not revealed effusion in the joint cavity. In order to relief the symptoms NSAID's and local cryotherapy of the joint 4 times daily for 15 minutes through an isolator were recommended. No protective antibiotic therapy was administered, due to in the all cases, the symptoms did not last more than one week. No allergic reaction, anaphylaxy and non-specific arthritis have been observed after 6 weeks from VS.

DISCUSSION

The aim of this study is to analyze the clinical effectiveness of the product ViscoPlus® Gel with objective statistical tools. Appropriate IAHA

product biophysical properties support a clinical orthopedic practice and reduce complications rate. The physicochemical properties of ViscoPlus® Gel were investigated in independent analysis by Lázaro et al., and showed it's advantage over other HA products. Viscoelastic properties of the HA preparations can be ordered according to the values of the rigidity, or vector sum of the elastic and the viscous modulus [21]. ViscoPlus® Gel was moreover an object of analysis of medium MW HA influence on in a robust *in vitro* culture of human-derived chondrocytes. Authors proved medium and high MW HA enhance chondrocytes proliferation and increase collagen type II (COL2A1), hypoxia-inducible factor 1α (HIF-1α) and chondroadherin (CHAD) expression [57]. High MW hyaluronan 2700 KDa in evaluation in the rat OA model 6 weeks after IAHA injection demonstrate a protective effect on cartilage by inhibiting aggrecanase expression [58]. IAHA economical effectiveness reaching 6,44 % of global cost of treatment indicate, in comparison to conventional support therapies, improved disease symptoms, joint function, quality of life and reduced direct treatment costs to avoid operative treatment or could be an option in failed conservative treatment preceding surgery [59, 60]. Concomitant therapy, mainly administration of chondroitin sulfate, NSAID's and steroids is associated with reduced local pain syndrome and functional normalization of musculoskeletal

system [61, 62]. In the research 60% of patients had adjuvant intraoral treatment mainly with NSAID with significantly better results after 6 weeks after VS injection.

In comparison PRP/HA VS a series of PRP injections should be considered a reasonable and acceptable alternative to HA injections for the treatment of symptomatic knee osteoarthritis [63, 64, 65]. This result is coherent with several studies which report that hyaluronan-based infiltration therapies are effective independently by the patient's disabilities but long effect could be achieved by combination therapy [66, 67, 68]. The literature reflects the current medical practice, and the reviews are "state-of-the-art" supporting the use of IAIHA products in the treatment of knee OA [69, 23]. Some authors do not find HA was non-inferior to three weekly injections of MWA in terms of pain reduction, and supports HA as an effective and safe treatment for knee osteoarthritis [70].

ViscoPlus® Gel 2,5% is a homogenous high molecular weight formulation that is administered as one 3-ml injection instead multiple 2 ml usually 1% given once every week. ViscoPlus® Gel 2,5% is manufactured by Bohus BioTech AB; Trädgårdsgatan 4, SE-452 31 Strömstad, Sweden it has been approved in Europe and also seeking approval in Asia and Latin America. In our study high MW HA product was therefore tested with subjective means of measurement, especially to analyze its capability of reducing joint pain symptoms and improving joint functions in the EVA and LAQ indexes. ViscoPlus® Gel is, so called "one shot" product, registered in EU market as sterile viscoelastic sodium hyaluronate solution for synovial injections, with approval to use in CE. As It follows is recommended for use in joint viscosupplementation in gonarthrosis and coxarthrosis. According to the evaluations the product has a higher relative efficiency for less severe arthritis, but the average relative effectiveness of around 0,4 for severe arthritis is still very high.

Cartilage protection of hyaluronic acid still remains to be proven. *In vitro* and on animal model experiments clinical efficacy shows 1-4 weeks' later onset than corticosteroids, but is maintained for 6 or even 12 months [71].

Contemporary injection to the joint needs proper equipment visualizing the process may be difficult in a non-swollen joint. In many experiences radiologic or ultrasound guidance is recommended and some tips and tricks may be helpful [72]. US guided intraarticular injections showed significantly higher accuracy rate than

injections in the blind injection in many papers [73, 74, 75]. The accuracy rate v.s blind attempts reaches 78% in plane technique (97%; $P < 0.05$) and out of plane method (95%; $P < 0.05$) and is superior to fluoroscopic guidance protecting from radiation [76, 77].

The efficacy of viscosupplementation is still ongoing debate, after discordant findings in some meta-analyses. Some poor results may be due to inappropriate use of HA injections, poorly adapted to the patient's OA phenotype [20]. Viscosupplementation is a treatment for chronic moderate symptomatic OA, and not for flares with joint swelling. Comparing short-term outcomes of HA injections with oral NSAIDs for treatment of knee OA, HA injections provided statistically significant but not clinically important improvements in knee pain and function, conservative management of degenerative meniscus lesions along with a lower overall risk of COX -1 inhibiting processes [78] This study supports the use of HA is clinically effective and enhances meniscus healing and reduces the need for partial meniscectomy at 1-year follow-up [79]. IAIHA for hip osteoarthritis were disappointing but promising in OA of the ankle and shoulder [80].

The rate of adverse reactions constituted 1,9% and had a mild course of treatment. In 5 cases, local redness, limited motion and stiffness of the joint, painful palpation of the injection site were confirmed usually are considered to be related to the injection [81]. In some severe cases the symptoms may simulate septic or pseud-septic arthritis where aspirated joint fluid examination, generally administered G- and G+ antibiotherapy and NSAID's are recommended [82, 83, 84]. Local adverse reaction causing unscheduled care in literature do not exceed 21% depending on series of injections. Second and next administrations have significantly lower rate of adverse events 1,28 – 0,9% and correlate with results of this study [85].

In VSAP special attention was put to infiltrate joint cavity without any resistance and pain manifested by a patient. Complications mostly are detected in a time of injection and are concerned with decompression and deposition in subcutaneous tissue or fat pad injected from infrapatellar - lateral approach. From author's experience in cases of post-operative treatment, joint adhesions, arthrotomies and arthroscopy any pain and disturbances during injection suggest to double check position of a needle in ultrasound. Non effused joints in obese cases are also skillness demanding attempts. Hypertrophic

synovium in course of rheumatic or crystallopathy patients can cause intrasynovial deposition of hydrogen causing severe pain and long-lasting discomfort with malfunction of the knee. Some needle maneuvers should be done to enter infrapatellar space and separate lamines of synovium, authors usually record the injection recording with patient ID.

Developing studies with multivariate MW HA division are needed to determine profile response and optimal VS treatment.

CONCLUSION

ViscoPlus® Gel as an HMW HA product injection, indicated in mild and moderate cases of OA, that in intraarticular administration improve joints mobility and decrease pain symptoms, what is firmly correlated with progressive and severe cases in medium-aged and elderly patients groups. That seems to be the target age of the IAIHA treatment what is consistent with the authors' long-term observations. The high score reduction in both analyses after treatment, accordingly EVA 6,6 and 5,7 in LAQ assessment scale was significant and constituted about 40% in the overall assessment of clinical improvement. During therapy no differences were notable after 6 weeks in men and woman groups visualized on probability density distribution where the LAQ scale separates pre-post patients better compared to EVA.

Low rate of adverse reactions 1,9 % was a final effect of many factors, including VSAP with particular emphasis on US guidance, standardized HMW HA, post-op indications and appropriate selection of the research and treatment group of patients. No allergic reaction and pseudo inflammatory processes after 6 weeks from IAIHA indicates the high safety of the procedure and the product. According to the results of the evaluation, ViscoPlus® Gel 2,5% can be considered as an effective method of treatment for medium term pain relief in case of mild and moderate OA,

as well as joint improving movement agent due to its efficient viscoelastic properties.

Additional clinical studies can settle the debate as to whether the HMW HA offers an advantage in long term observations and their place in OA contemporary treatment.

Acknowledgements

Authors' contributions

AG contributed to the study design, VS treatment, analysis, and interpretation of data. PD contributed to the study design, analysis, and interpretation of data. PT contributed to the study design and interpretation of data. SG contributed to the study analysis, and interpretation of data. All authors read and approved the final manuscript.

Founding

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Availability of data and materials

All research data are available from the Orthopedic Department, Jurajska Medical Center, Czestochowa, Poland

Ethics approval and consent to participate

The permission for the implementation of our study was not needed in case of post treatment analysis.

Consent for publication

Not applicable.

Competing interests/ Conflict of interest

The authors declare that they have no competing interests.

Contributor Information

Artur Gap; flydoctorgap@gmail.com

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