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Surgical Research

SAVETYAL, There Are Benefits in Choosing A Handy Middle-Molecular-Weight Hyaluronic Acid Formulation

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ABSTRACT

Introduction: *Viscosupplementation with high-molecular-weight hyaluronic acid does not offer efficacy and quality-of-life benefits compared to middle-molecular-weight hyaluronate formulations for intra-articular injection. Moreover, high-molecular-weight hyaluronic acid might have some biophysical liabilities. The paper reports the outcomes of a purely observational survey after a previous intra-articular treatment to simulate the real-world experience of patients and orthopaedics specialists with a middle-molecular-weight hyaluronate medical device in the general population of knee osteoarthritis patients.*

Methods: *Evaluations based on patient-assessed "Knee injury and Osteoarthritis Outcome Score" (KOOS) and investigator-assessed "Range Of Motion" (ROM). Primary efficacy endpoint: patient-assessed pain during selected daily activities at T1 and T2 vs baseline (T0); secondary efficacy endpoint: patient-assessed changes in four KOOS daily activities and investigator-assessed ROM limitations at T1 and T2 vs T0.*

Results: *The reduction of surveyed mean KOOS pain and function scores at T1 and T2 vs T0 was almost always highly significant for all surveyed pain categories—for instance, the mean "Straightening/Bending knee fully" pain score fell from 1.9 ± 0.85 to 0.8 ± 0.91 (–57.9%), the mean "Going upstairs/downstairs" pain score from 2.0 ± 0.69 to 0.9 ± 0.92 (–55.0%), the mean "Going upstairs/downstairs" function score from 2.0 ± 0.83 to 0.9 ± 1.01 (–55.9%), and the mean "Walking on flat surface" function score from 1.8 ± 0.97 to 0.9 ± 1.01 (–50.0%). The scores of all surveyed pain and function categories further improved significantly between the first and final follow-ups. ROM scores also showed a tendency to increase.*

Discussion: *The survey study confirms the persisting value of the intra-articular SAVETYAL middle-molecular weight hyaluronic acid, with a confirmed clinically meaningful and statistically significant relief of pain and difficulties in daily life. The likely cognitive bias intrinsic to the survey design does not weaken the robust objective (investigators) and subjective (treated patients) outcomes.*

Keywords

Knee osteoarthritis, KOOS, Middle-molecular-weight hyaluronic acid, High-molecular-weight hyaluronic acid, Range of Motion, Viscosupplementation.

Introduction

Across the world, an estimated 240 million people currently suffer from osteoarthritis, with years lived with disability increased by 31.4% between 2007 and 2017. The disease prevalence is steadily rising because of worldwide ageing and the increasing incidence of obesity in rich and developing countries [1,2]. Regarding knee osteoarthritis, current global prevalence and incidence estimates run at 16% and 203 per 10,000 person-years, respectively [3]. Together with lifestyle changes (physical therapy, exercise, weight

loss), the standard of care includes acetaminophen (paracetamol), non-steroidal anti-inflammatory drugs and COX-2 inhibitors, and possibly tramadol and intra-articular steroids [4]. Concomitantly, viscosupplementation with intra-articular hyaluronic acid of variable molecular weight (IAHA) has increased worldwide acceptance for over twenty years. The main reason for the IAHA's success is joint pain relief with no systemic side effects [4].

Several systematic reviews and meta-analyses of randomised clinical trials do not confirm the IAHA benefits for physical function and pain management suggested by clinical studies. Still, the American Academy of Orthopaedic Surgery (AAOS), after recommending against the routine use of IAHA for knee osteoarthritis, has only recently softened its stance to a moderate recommendation in its clinical practice guideline 2021 update [5]. Osteoarthritis specialists trust the IAHA viscosupplementation efficacy. In a recent survey, 65.7% of respondents qualified IAHA as moderately or highly effective in knee osteoarthritis, with only 22.1% of surveyed specialists deeming it ineffective [6]. Moreover, as recently shown by a recent international Google trends analysis, public interest in IAHA for knee osteoarthritis is rising in Europe and the United States [7], confirming previous favourable patient-reported outcomes [8,9].

Head-to-head studies seem to confirm that high-molecular-weight IAHA (≥3,000 kDalton or KDa) are consistently more effective than low-molecular-weight sodium hyaluronate preparations (less than 1,000 kDa) [10]. Conversely and interestingly, high-quality head-to-head studies of middle-molecular-weight IAHA (1,000 kDa to less than 3,000 kDa), compared with the much-hyped high-molecular-weight preparations, do not show differences in improving primary outcome measures. These were the outcomes for pain evaluated at six months with the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) in 660 knee osteoarthritis patients in a single-blind multicentre study of high- and middle-molecular-weight IAHA. It was also the outcome for the improved WOMAC physical function and stiffness scores from the one-month follow-up until the final sixth-month follow-up visit in 72 patients [11,12]. Of seven head-to-head studies comparing medium- and high-molecular-weight IAHA preparations, none reported any difference in efficacy and quality of life parameters like the WOMAC index, Visual Analogue Scale (VAS)-measured pain, Hospital for Special Surgery (HSS) knee score, and Short Form Health Survey (SF)-36 [10]. Moreover, with no real efficacy benefits, high-molecular-weight IAHA have a longer relaxation time (time to transition from a mainly viscous behaviour to an elastic one), meaning high-molecular-weight formulations need more time for their three-dimensional network to untwine and develop a predominantly elastic behaviour [13]. Still, elasticity is a vital need for artificial synovial fluids to successfully absorb mechanical burdens, restore the rheological conditions of joints, and preserve cartilage from damage or fretting [13].

The paper reports the outcomes of an observational survey in real-world knee osteoarthritis patients with no active intervention and no selection criteria but hypersensitivity to ingredients and excipients after a previous IAHA treatment with a middle-molecular-weight hyaluronate medical device to simulate the device's real-world use in the general population of knee osteoarthritis patients. An anonymous questionnaire, distributed to orthopaedics specialists who were already familiar with the surveyed medical device, was the tool to cast light on the experiences and sensations of patients and specialists.

The survey study was the first in a long-term monitoring program of the persisting performance and safety of a proprietary IAHA medical device within the device's post-marketing clinical follow-up (PMCF) program required by the European Union regulatory authorities. Confirming the profile of known side effects and contraindications and identifying any unknown side effects or emergent risks of the IAHA device was, and will be, another purpose of the survey and the long-term monitoring program. Resorting to real-world data independent from the tight inclusion and exclusion criteria of randomised clinical studies with their highly selected patient samples is the clue that supports the value of the investigation.

Materials and Methods

Survey Design

The survey's single-arm multicentre retrospective cohort comprised adults of both genders seeking relief for osteoarthritis pain and functional disability who had previously undergone a three-session, intra-articular treatment cycle with the surveyed Class-III CE-mark IAHA medical device. The anonymous questionnaire designed for the survey after the IAHA treatment cycle, while not allowing personal identifications, allowed the four investigators who performed the post-treatment survey to collect information about the surveyed medical device thoroughly, faithfully, rapidly, and without time constraints. The questionnaire included information on demographics, knee disease stage (Kellgren Lawrence score, Table 1), knee(s) affected, and concomitant use of other drugs.

Table 1: The Kellgren-Lawrence Classification System for knee osteoarthritis.

Grade 0	No joint space narrowing (JSN) or reactive changes
Grade 1	Possible osteophytic lipping + doubtful JSN
Grade 2	Definite osteophytes + possible JSN
Grade 3	Moderate osteophytes + definite JSN + some sclerosis + possible bone end deformity
Grade 4	Large osteophytes + marked JSN + severe sclerosis + definite bone end deformity

SAVETYAL (Mastelli S.r.l., Sanremo, Italy), the brand name of the surveyed IAHA device, is certified for relieving painful degenerative, post-traumatic diseases or alterations of joints, including the knee. The SAVETYAL functional ingredient (40 mg/2mL of highly purified, non-cross-linked monobasic hyaluronate sodium phosphate of biotechnological origin; molecular weight: 1,200-1,500 kDa) is formulated as a sterile fluid

gel (PLAY SURE DOPING FREE certified) in phosphate buffer (pH, 6.5-7.5) in 2-mL prefilled syringes [14,15]. The disposable syringes should be used with 18- to 22-gauge Luer-tip needles, usually 20G (not in the commercial package). The retrospective survey respected the Helsinki Declaration and Good Clinical Practice principles. The study protocol and study materials were preliminarily peer-reviewed for ethical problems.

Survey Efficacy Assessments

Patient-assessed "Knee injury and Osteoarthritis Outcome Score" (KOOS) reduced questionnaire

The first description of the validated KOOS questionnaire was in 1998 as an extension of the WOMAC Osteoarthritis Index, designed to assess the patients' subjective opinions about their knee injuries and osteoarthritis. More than twenty studies have validated the robust KOOS properties based on standardised answer options, with scores ranging from 0 to 4. Because of the high non-response bias of too-long questionnaires and the survey nature of the study, the investigators decided to use only a selection of the KOOS Pain questions *[straightening and bending knee fully, walking on a flat surface, sitting or lying, going up and down stairs]* and KOOS Function questions *[descending and ascending stairs, rising from sitting, standing, walking on a flat surface]* overlooking other questions and any total KOOS score [16].

Investigator-assessed "Range Of Motion" (ROM)

The knee Ranges Of Motion (ROM) functionally needed in typical daily activities are 0° to 65° for walking, 0° to 85° for climbing stairs, 0° to 90° for descending stairs, 0° to 90° for sitting down, 0° to 95° for standing up from sitting, 0° to 105° for tying shoelaces, 0° to 75° for picking an object from the floor, 0° to 115° for riding a bike, and 0° to 115° for sitting cross-legged [17]. For the survey's sake, ROMs were graded at T0, T1, and T2 on a five-step nominal scale and a Likert-like five-score (from 0 to 4) scale, as illustrated in Table 2.

Table 2: ROM nominal and semi-quantitative scoring system adopted for the post-SAVETYAL survey.

Very Poor Flexion (less than 80°)	Score 0
Poor Flexion (80° to 95°)	Score 1
Manageable Flexion (96° to 109°)	Score 2
Good Flexion (110° to 120°)	Score 3
Great Flexion (More than 121°)	Score 4

Primary efficacy endpoint

— Osteoarthritis-related, patient-assessed changes in knee pain at T1 and T2 *vs* T0 while performing the four everyday activities selected for pain evaluation [see "Patient-assessed 'Knee injury and Osteoarthritis Outcome Score' (KOOS) reduced questionnaire" paragraph]. Five-score assessment scale: 0 ("No pain"), 1 ("Mild pain"), 2 ("Moderate pain"), 3 ("Severe pain"), 4 ("Extreme pain").

Secondary efficacy endpoint

— Patient-assessed changes at T1 and T2 *vs* T0 in the four daily functions selected for function evaluation [see "Patient-assessed 'Knee injury and 'Osteoarthritis Outcome Score' (KOOS) reduced questionnaire" paragraph]. Five-score assessment scale (over the previous week): 0 ("No pain"), 1 ("Mild pain"), 2 ("Moderate pain"), 3 ("Severe pain"), 4 ("Extreme pain").

— Investigator-scoring of ROM limitations at T1 and T2 *vs* baseline T0 session.

Five-score outcome scales have several statistical benefits: for instance, unimodal and symmetric distributions. Conversely, scales with a higher number of scores have highly skewed J and U-shaped distributions. Outcomes assessed on limited-point scales also have lower means and floor and ceiling effects, and regression analysis shows that limited-score scales account for a significant fraction of total variance in floor and ceiling effects. Moreover, limited-point scales minimise the contribution of unaccounted factors [18].

Planned assessment procedures and techniques by independent evaluators

- T0 session [kick-off: baseline evaluation and first SAVETYAL injection]:
  - → Patient's demographics and baseline knee osteoarthritis assessment.
  - → Compilation of the reduced KOOS questionnaire by the surveyed patient.
  - → ROM assessment by the investigator.
- T1 session [before the second SAVETYAL injection three months after T0]:
  - → Compilation of the KOOS-like questionnaire by the surveyed patient.
  - → ROM assessment by the investigator.
  - → Side effects, if any (see "Safety assessment" paragraph for details).
- T2 session [before the third SAVETYAL injection six months after T0]:
  - → Compilation of the reduced KOOS questionnaire by the surveyed patient.
  - → ROM assessment by the investigator.
  - → Side effects, if any (see "Safety assessment" paragraph for details).

Safety assessments

Structured safety interviews by the investigators (Likert-like four-point scoring scales from 0 to 3), planned at T1 and T2 sessions, to investigate the clinical presentation and severity of known side effects, unknown adverse events or emergent risk. Moreover, the investigators questioned the subjects about safety problems at each treatment session.

Spontaneous reporting by phone or e-mail: strongly recommended throughout the study.

Sample size

Pre-study estimate (G*Power statistical program version 3.14) of thirty-nine knee osteoarthritis patients, assuming a 90% power of avoiding false-negative type II errors (ß=0.10) in inferences about mean total score changes [19]. Already published data on

the efficacy of similar intra-articular hyaluronic devices led to an estimated effect size of 0.6 and were the basis for the sample estimate [20,21]. For further caution, the investigators planned for a survey cohort larger than the statistically adequate estimate.

Inferential statistics

Software: StatPlus, statistical analysis program Version v7 [22]. Tabulations: means ± standard errors of the mean (SEM) for descriptive variables; frequencies and percentages for qualitative variables. The semi-quantitative nature of the T1 and T2 vs T0 score outcomes suggested an inferential non-parametric approach like the Mann-Whitney test for two categorical independent groups. Significance threshold: set at 0.05 for two-sided tests.

Results

Table 3 illustrates the demographics and clinical baseline situation of the survey cohort of 46 real-world patients with knee osteoarthritis of at least grade-one severity and less than grade five. SAVETYAL intra-articular treatment was in the right knee in 30 patients and the left knee in 29 (sides of three injected knees unknown); 16 patients received treatment bilaterally (overall total; 62 knees treated intra-articularly). Twenty-eight patients reported other concomitant therapies, NSAIDs 17, chondroprotectors for 6, and previous knee surgery for 2.

Table 3: Demographics of the surveyed knee osteoarthritis patients (upper table; SEM = standard error of the mean) and baseline severity of injected knees (lower table).

Cohort demographics (46 real-world patients)		
Age (whole cohort)	Mean (years ± SEM)	65.6 ± 12.95
	Median (years)	68.0
	Range (years)	29 to 86
Gender	Female (n, %)	30 (65.2%)
	Male (n,%)	16 (34.8%)
Weight	kg (mean ± SEM) *	77.1 ± 19.63
Height	meters (mean ± SEM) **	1.65 ± 0.10
* Sample estimate on 37 patients, ** Sample estimate on 27 patients		
Baseline severity of knee osteoarthritis out of 62 injected knees		
Grade 1	9 (14.5 %)	
Grade 2	23 (37.1 %)	
Grade 3	22 (35.5 %)	
Grade 4	7 (11.3 %)	
Unknown	1 (1.6 %)	

Figure 1 shows the distribution of received injections in the 62 treated knees, often less than the suggested treatment cycle in the SAVETYAL product information leaflet (one weekly intra-articular infiltration for 3 to 5 weeks) [14].

KOOS Pain Scores

The reduction of surveyed mean KOOS pain scores compared to baseline (T1 vs T0 and T2 vs T0) was almost always highly significant for all surveyed pain categories at both assessment sessions. Compared to T1, all surveyed pain categories improved further and significantly at the final T2 follow-up (Figure 2).

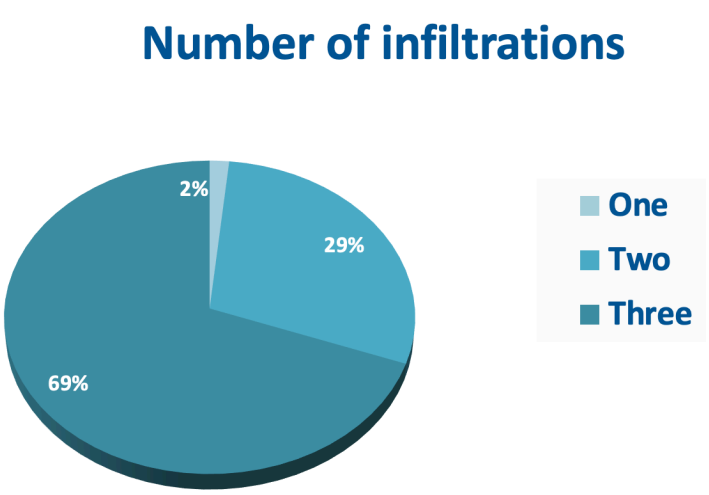

Figure 1: Distribution of the number of intra-articular injections in the retrospective cohort of 62 knees with osteoarthritis of variable severity treated with SAVETYAL.

The reduction of surveyed KOOS function scores compared to baseline (T1 vs T0 and T2 vs T0) was also significant or highly significant. Compared to T1, the further improvement at T2 was again significant (Figure 3).

Range of Motion changes

Figure 4 illustrates the ROM changes with SAVETYAL treatment in all treated knees with baseline ROMs less than 5. At the end of follow-up (T2), all ROM categories tended to improve, although without reaching the statistical significance threshold.

Safety

Side effects similar to those commonly reported with similar IAHA devices, generally mild, expected and strictly related to the injection procedure, occurred only at the injection site; pain and local swelling were the most frequently reported and the (relatively) most disturbing (Table 4). All inconvenience and temporary discomfort resolved rapidly and spontaneously with no need for further treatments.

Table 4: Observed side effects out of 62 injection sites: overall incidence and incidence of clinically moderate (score 2) and clinically severe (score 3) events according to the investigator's evaluation.

Side effect	Incidence (%)	Presentation (% of patients)	
		Clinically moderate	Clinically severe
Local pain	41.9	21.0	8.1
Local swelling	21.0	1.6	—
Local redness	8.1	—	—
Heat sensation	9.7	—	—
Burning	9.7	—	—

Discussion

The pain of knee osteoarthritis, the most common chronic degenerative joint disease, and related reduced activity can weaken the quadriceps, biceps femoris and other hamstring muscles, leading to increased instability. Contrary to the AAOS

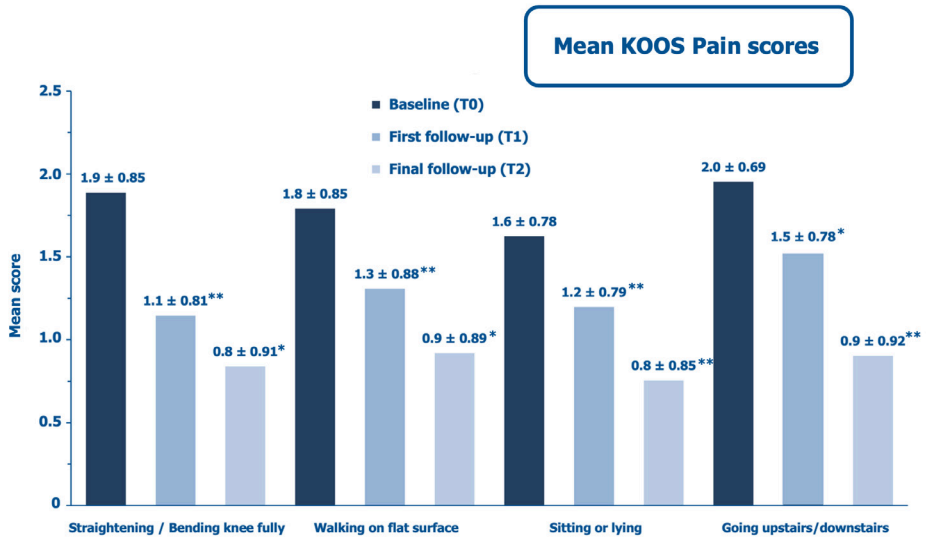

Figure 2: Mean scores (± SEM) from a selection of questions in the KOOS Pain section (* p <0.05 and ** p <0.01 vs baseline).

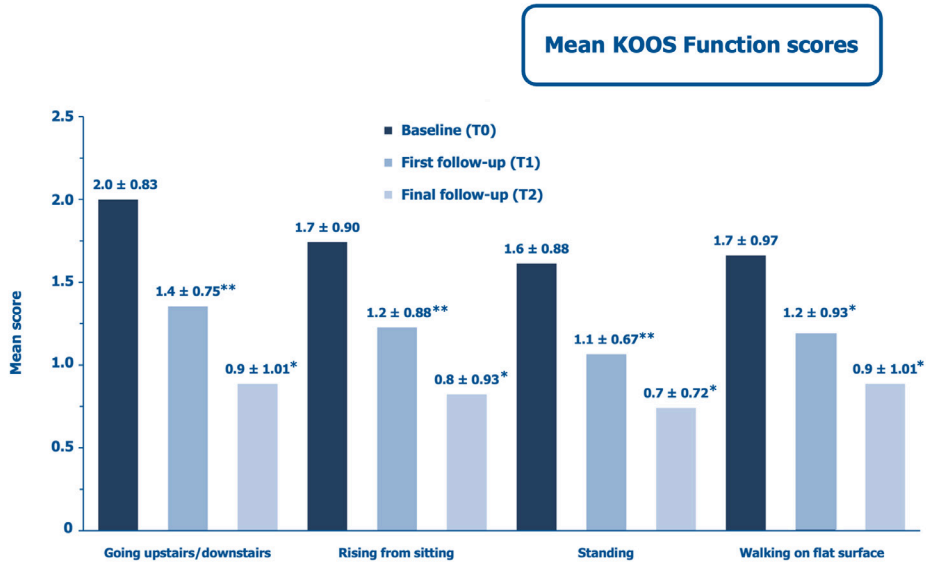

Figure 3: Mean scores (± SEM) from a selection of questions in the KOOS Function section (* p <0.05 and ** p <0.01 vs baseline).

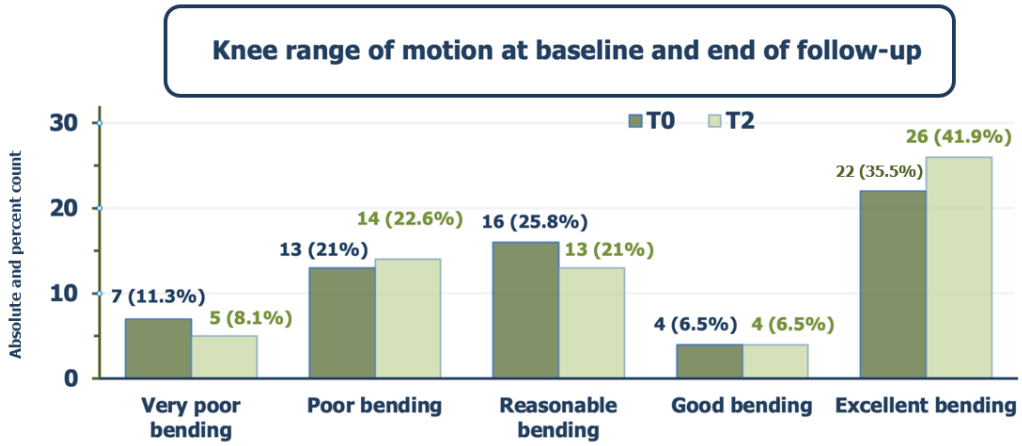

Figure 4: ROM changes with SAVETYAL treatment in the 62 treated knees with baseline ROMs less than 5 over the follow-up period: number and per cent of patients with knee osteoarthritis in each ROM category at T0 and T2.

clinical practice guideline before 2021, the EULAR (European League Against Rheumatism) and ACR (American College of Rheumatology) guidelines have long recommended IAHA as knee osteoarthritis treatment, thanks also for delaying the need for total knee replacement surgery [5,23].

With self-commenting outcomes, the survey study confirms the known evidence about the persistent value of the SAVETYAL middle-molecular-weight hyaluronic acid—steady, clinically meaningful relief of pain and difficulties in daily activities over the six-month follow-up period with three-month-spaced intra-articular injections. Both surveyed investigators and treated patients expressed personal satisfaction, with scores for the surveyed selection of KOOS pain and function questions ranging between –57.9% and –50.0% between baseline and end of the study. The admittedly large standard errors of the mean, highlighting the variability of answers typical of surveys, do not signal methodological liabilities or weaken the evidence of perceived objective and subjective benefits.

A survey may look like a rudimentary tool to investigate objective and subjective outcomes in treating knee osteoarthritis, but this may be a misperception. The survey is a patient-centred tool that lets the patient feel an actual partner in the physician/patient's alliance [24]; moreover, the pain and function benefits at first and second follow-up sessions are too consistent and shared by patients and investigators to be only an efficacy delusion.

The survey design has several liabilities—for instance, a cognitive bias may likely lead to overestimating the benefits in a condition that is often excruciating. Moreover, there was no attempt at a control group, which might have helped to look at quantitative outcomes in perspective. Still, the study aimed to monitor and confirm the efficacy and safety profile of SAVETYAL in knee osteoarthritis intra-articular treatment and this purpose was successfully attained.

References

1. Wu YZ, Huang HT, Ho CJ, et al. Molecular weight of hyaluronic acid has major influence on its efficacy and safety for viscosupplementation in hip osteoarthritis: a systematic review and meta-analysis. Cartilage. 2021; (1_suppl): 169S-184S.
2. GBD 2017 DALYs and HALE Collaborators. Global, regional, and national disability-adjusted life-years (DALYs) for 359 diseases and injuries and healthy life expectancy (HALE) for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet. 2018; 392: 1859-1922.
3. Cui A, Li H, Wang D, et al. Global, regional prevalence, incidence and risk factors of knee osteoarthritis in population-based studies. EClinicalMedicine. 2020; 29: 100587.
4. Honvo G, Reginster JY, Rannou F, et al. Safety of intra-articular hyaluronic acid injections in osteoarthritis: outcomes of a systematic review and meta-analysis. Drugs Aging. 2019; 36: 101-127.
5. The American Academy of Orthopaedic Surgeons Board of Directors. Management of Osteoarthritis of the Knee (Non-Arthroplasty), Evidence-Based Clinical Practice Guideline, August 31, 2021.
6. Alnasser S, AlHussain F, Asiri H, et al. Orthopedic surgeons' views of hyaluronic acid formulations in the management of knee osteoarthritis: a questionnaire-based cross-sectional study. Medicina (Kaunas). 2021; 57: 990.
7. Cohen SA, Brophy RH, Chen AF, et al. Public interest in hyaluronic acid injections for knee osteoarthritis in the United States and Europe: an international Google trends analysis. Arthroplast Today. 2022; 18: 157-162.
8. Gusho CA, Jenson M. Patient-reported outcomes of short-term intra-articular hyaluronic acid for osteoarthritis of the knee: a consecutive case series. Cureus. 2019; 11: e4972.
9. Mochizuki T, Ikari K, Yano K, Okazaki K. Comparison of patient-reported outcomes of treatment with low-and intermediate molecular weight hyaluronic acid in Japanese patients with symptomatic knee osteoarthritis: a prospective, randomised, single-blind trial. Asia Pac J Sports Med Arthrosc Rehabil Technol. 2020; 21: 22-26.
10. Webner D, Huang Y, Hummer CD 3rd. Intraarticular hyaluronic acid preparations for knee osteoarthritis: are some better than others?. Cartilage. 2021; 13: 1619S-1636S.
11. Juni P, Reichenbach S, Trelle S, et al. Efficacy and safety of intraarticular Hylan or hyaluronic acids for osteoarthritis of the knee: a randomised controlled trial. Arthritis Rheum. 2007; 56: 3610-3619.
12. Kotevoglu N, Iyibozkurt PC, Hiz O, et al. A prospective randomised controlled clinical trial comparing the efficacy of different molecular weight hyaluronan solutions in the treatment of knee osteoarthritis. Rheumatol Int. 2006; 26: 325-30.
13. Snetkov P, Zakharova K, Morozkina S, et al. Hyaluronic acid: the influence of molecular weight on structural, physical, physico-chemical, and degradable properties of biopolymer. Polymers (Basel). 2020; 12: 1800.
14. SAVETYAL product information leaflet /Instructions For Use.
15. Sodium Hyaluronate EP Altergon, Safety Data Sheet, 15/04/2021.
16. Sahlqvist S, Song Y, Bull F, et al. Effect of questionnaire length, personalisation and reminder type on response rate to a complex postal survey: randomised controlled trial. BMC Med Res Methodol 2011; 11: 62.
17. Holla JF, Steultjens MP, van der Leeden M, et al. Determinants of range of joint motion in patients with early symptomatic osteoarthritis of the hip and/or knee: an exploratory study in the CHECK cohort. Osteoarthritis Cartilage. 2011; 19: 411-419.
18. Garratt AM, Helgeland J, Gulbrandsen P. Five-point scales outperform 10-point scales in a randomised comparison of item scaling for the Patient Experiences Questionnaire. J Clin Epidemiol. 2011; 64: 200-207.

19. Faul F, Erdfelder E, Buchner A, Lang A-G. Statistical power analyses using G*Power 3.1: Tests for correlation and regression analyses. Behav Res Methods. 2009; 41: 1149-1160.
20. Chavda S, Rabbani SA, Wadhwa T. Role and effectiveness of intra-articular injection of hyaluronic acid in the treatment of knee osteoarthritis: a systematic review. Cureus. 2022; 14: e24503.
21. Altman R, Hackel J, Niazi F, et al. Efficacy and safety of repeated courses of hyaluronic acid injections for knee osteoarthritis: a systematic review. Semin Arthritis Rheum. 2018; 48: 168-175.
22. Statistical software downloaded from https://www.analystsoft.com/en/products/statplus/#statfeatures.
23. Altman R, Lim S, Steen RG, et al. Hyaluronic acid injections are associated with delay of total knee replacement surgery in patients with knee osteoarthritis: evidence from a large U.S. health claims database. PLoS One. 2015; 10: e0145776.
24. Sahlqvist S, Song Y, Bull F, et al. Effect of questionnaire length, personalisation and reminder type on response rate to a complex postal survey: randomised controlled trial. BMC Med Res Methodol. 2011; 11: 62.