INTRAARTICULAR THERAPY IN HIP OSTEOARTHRITIS. REASONS FOR THE VARIABILITY OF THE RESULTS OF INTRAARTICULAR THERAPIES

L. Sapundzhiev, T. Sapundzhieva

Rheumatology Department, University Hospital "Pulmed"
Department of Propedeutic of Internal Diseases, Medical Faculty, Medical University – Plovdiv

Abstract. *The presented review consists of 2 parts: descriptive and systemic analysis. In the first part mechanisms of action, indications, contraindications, methods of administration and adverse effects of intraarticular corticosteroids (IACS) are described, as well as the most common used in the studies on intraarticular therapy comparators, such as natural saline (NS) and local anesthetics (LA). Also the official statements and recommendations of the rheumatologic organizations (EULAR; ACR; OARSI) are quoted. In the systemic review 20 original studies on IACS in HOA are analysed. The data of rapidity, expression and sustainability of the effects of IACS are assessed by meta-analyses, the obtained results are compared to those of the open 4 descriptive and 4 systematic reviews of foreign authors. In the discussion the different interpretations of the results from the original studies and preceding meta-analyses are pointed out according to the authors' opinion.*

Key words: *hip joint, intraarticular therapy, corticosteroids*

Intraarticular therapy in OA and in particular in HOA is important, because it is directed to the concretre joint. It gives the opportunity the therapeutic local concentrations of the active substances to be reached with minimal systemic and/or side effects [1, 2]. In addition the arthrocentesis, accessing the articular cavity, gives opportunity for the performance of diagnostic (aspiration and investigation of synovial fluid, contrasting) and therapeutic (articular lavage) procedures.

The problem with the hip joint (HJ) is its deep anatomical location and proximity to the neuro-vascular bundle of femur. The arthrocenteses of HJ according to the technique are classified into "blind" – with the help of anatomic vectors and preceding radiographs and "guided" arthrocenteses with a direct visualization of the course of the needle into the joint cavity.

The methodology of the "blind" arthrocenteses includes 2 accesses – anterior and lateral [3-6], accuracy studies establish on average 60% accuracy of the anterior and 80% for the lateral access. Other authors [7] report the accuracy of the lateral access to reach 90%. My own study [8], comparing the accuracy of the blind lateral access to US-guided antero-sagital access and the lateral access under radiographic control establish a definite categoric dependence of the accuracy of the blind access on the radiographic classK/L and BMI. The accuracy in K/L II-74%, in K/L-III – 61.3% and in K/L-IV – 40%. At the same time US – guided arthrocenteses showed accuracy as follows: K/L-II – 100%; K/L-III – 100%; K/L-IV – 93%.

The major rheumatologic organisations (ACR; EULAR; OARSI) in their recommendations for the management of HOA categorically require the use of the guided arthrocenteses without any preferences, referring to the method of guidance [10-13].

The guided arthrocenteses are classified into US guided or X-Ray guided.

X-ray guidance is following perfectly the course of the needle to the selected site, but it requires a contrast substance for the verification of the intraarticular location [9]. Diracoglu et al. In 2009 prove that only 29 from 38 – „precise" positions of the needle under X-ray control have been accurate after injecting a contrast substance. X-ray guidance is "slower" and "more expensive" method, compared to US-guidance and is accompanied by a significant radiation exposition of the operator and the patient [8]. Besides, analogous to the administration of NS-normal saline, which is with a proven effect on the pain during lavage, in iodine containing contrast substances, especially during repeated administrations despite of the low volume (1 ml), are possible serious adverse effects especially during a continuous follow up. That is why at present X-ray guidance is used only in cases, requiring contrast substance administration (fistulisation after a joint replacement) and in other rare indications.

US-guidance is with a high accuracy, a shorter duration and lower cost in the absence of adverse effects for the patient and the operator. Because of the popularisation of the method among the rheumato-

logic society worldwide and in Bulgaria the rheumatologists have a better ability to use US-guidance for diagnostic and therapeutic purpose, totally replacing the X-ray guidance technique. Difficulties in US guided arthrocenteses are rarely met – in combination of a high BMI ≥ 32 with a high K/Lclass IV, as well as serious flexor-adductor contractures due to the bad acoustic window and the problematic operative field.

Basic classes of medications for an intraarticular therapy, mechanism of action, indications, contraindications, therapeutic and adverse effects

1) ***Natural saline (NS)*** – used long time as a comparator in clinical trials, treating the effects upon the basic groups of medications. The results of many studies, however showed:

√ NS – possesses placebo effect [2, 15-17], with a therapeutic range (0.144; p = 0.020).

√ NS – possesses also an own real therapeutic effect with short therapeutic range (0.29; CI-95%; 0.04-0.54). This effect is probably due to the dilution of the toxic products, damaging of AC, SB, ST and of the inflammatory cytokines in the synovial cavity [14-16]. This effect consists of significant changes of the rate of pain, lasting up to 3 months (reported in 99% of the studies, used NS) – up to 2months (reported in some studies for KOA). The therapeutic range and the persistent effect of NS have shown a dependence on the radiographic class and the final evaluated parameters are highly overpassing the pure placebo effect (0.144; p = 0.020). Naturally, in this context the question is evoked – which substance to be used as a comparator in control groups –pure puncture as is reported in several studies [17], but how many ethic commissions should permit a similar design in times of a market orientated medicine and hospital policy?

2) ***Local anaesthetics (LA)*** – initially used intra-articular for differentiation of the origin of regional pain – HJ/vertebral column. Later they are used similarly to NS as comparators or as separate therapeutic groups in a large number of studies in HOA [20, 22, 24, 27-29, 31-35, 38]. Mostly used are 4 molecules: Lidocaine 05-1%; Bupivacaine 0.5-1%; Mepivacaine 0.5-1%; Ropivacaine 0.5-1%.

√ Of great importance during the application of LA is the concentration of the solutions – it is established that 0.5-1% solutions have a neutral or positive effect on the metabolism of AC; SB; ST, while 2% solutions of Lidocaine, Bpv, Mpv, and probably of Rpv exert a negative effect on the joints, shortening the “natural evolution” (accelerate the radiographic progression after an initial favourable effect – compared to controls with NS) [36, 38].

√ Therapeutic range of LA and the lasting effect similar to those of NS, are function of the radiographic class K/L and the exit values of the followed parameters, but not dependable on the molecule used (Bpv, Mpv or Lidocaine) [2, 20, 22].

3) ***Intraarticular corticosteroids (IACS)*** – widely used because of the opportunity for a direct effect on the damaged joint with minimal systemic and side effects, typical for this group. The actual recommendations by the major rheumatologic organisations: EULAR [12] – from 2005; OARSI [11] – from 2008; ACR [13] from 2012; OARSI [14] – from 2019. and include the use of IACS при HOA, despite of several remarks (ACR expert panel). “Because of the low number of randomized and placebo controlled studies in patients with HOA, our recommendations are based on the estimation that patients with HOA – should be treated in the same way as these with KOA“. The last recommendations of OARSI 2019 for a nonsurgical treatment of KOA, HJ and polyarticular damage approveIACS – only during the flares of the disease, for short termed (4-6 weeks) improvement of pain and actually only of the knee joint [13]. Naturally the recommendations reflect the worldwide knowledge of the problem at the time of their creation according to their authors; views. 20 years after the issues look more different, i.e.:

√ Development of new forms IACS – (triamcinolone acetonide extended release with microsphere technology) – permitting dosed, sustained release of the active substance, keeping therapeuticintra-articular concentrations in SF ≥ 12 weeks, while the systemic serum concentrations are not different from these of the classic formula TcA.

√ The acceptance of the inflammation as a component in the pathogenesis of HOA, associated directly with the disease progression, as well as using the modern techniques for visualization (PwDPP-US) to detect fast and surely its presence or absence in the articular cavity at a present moment – is posing this group of medications on the first line along with the classic NSAIDs.

Mechanism of action of IACS – they realize their effects by genomic and nongenomic mechanisms. The genomic ones are mediated by the cytosolic glucocorticoid receptor and result intransactivation or transrepression of regulatory proteins, that control the synthesis and the release of the proinflammatory cytokines. Non genomic mechanisms are presented by the release of specific proteins by the cytosolic

protein complex after binding to CS or direct membrane effects. The final result is an impact over all the inflammatory cells and with their help modifying the production and release of key cytokines (↓ IL-1β; IL-2; IL-3; IL-6; IL-17; TNF-α; γ-INF; ↑ IL-4; IL-10; IL-13), (↓) phospholipase A2, COX – pathways and prostaglandins, leukotrienes and NO synthesis [37].

Medications and doses – The most common used най-често IACS are:

√ Methylprednisoloneacetate – Depo Medrol Phyzerfl. 40 mg/ml; 80 mg/ml.

√ Betamethasonedipropionate – 6.43 mg/2.63 mg – betamethasone sodium phosphate – Diprofos amp. 7 mg/1 ml – MSD; Flosteron amp. 7 mg/1 ml – KRKA; Clestone Chrondose amp. 1 ml – 5.7 mg/3.9 mg – MSD

√ Triamcinolon acetonide – Kenalog USP 40 mg/ml.

√ Triamcinolon hexacetonide – Aristospan USP amp. 20 mg/ml.

Administration – the general rule for IACS is: not more than once/3 months, not more than 3 applications per year, not more than 40 mg as a single dose. Below are presented the most commonly used IACS.

Side effects of IACS

√ Local reactions – on the site of application, the most serious of which is

a) Iatrogenic articular infection, rare – reported incidence 1/50 000 in some articles [39-49].

b) Others – frequent reactions are the regional post injection flares, manifested by a pain, local warmness and even erythema of the overlying skin,-successively imitating septic arthritis,the microscope and cultural investigation of synovial fluid do not verify any infection. These “flares: are frequent, according to some authors – to 26% of the patients manifest such reactions at a different extent [39-49], fortunately – they are transitory with a spontaneous or assisted recovery for a period of 76 hours.

c) Dermal hypopigmentation and local atrophy of the subcutaneous fatty tissue – observed more frequent in triamcinoloneextra-articular application late complications, developing 1-3 months after the procedure [41-49].

d) Development of RPHOA – rare in inappropriate application in atrophic models, or frequent repeated applications [41-50].

e) Increasing of the risk of infection prior to an arthroplasty [31, 51], despite of the lack of direct proofs, principal statement is to be avoided IACS 3 months prior to the procedure.

√ Systemic side effects – transitory, rarely serious, frequent – observed in 15% of the patients. They include flushing of the face, V region erythema, observed 2-24 hours after the injection rarely staying more than 36 h., raising of BP and blood glucose for 3-5 days after the injection. The patients should be informed of these possible adverse events, especially the diabetics and those with an increased cardiovascular risk.

Contraindications for IACS

√ The most important is the presence or suspicion for a local – intraarticular, the overlying skin or a systemic infection. Basic principal is the injections not to be performed through any skin lesions.

√ Haemorrhagicdiatheses – thrombocytopenia, thrombocytopathies, coagulopathies, systemic anticoagulant therapy. Combined therapies with clopidogrel and aspirin, as well as the new anticoagulants – direct inhibitors of factor Xa-rivaroxaban (xarelto); apixaban (eliquis); dabigratan (pradaxa), especially combined – should also be avoided.

√ By the result Not controlled arterial hypertension or diabetes mellitus.

√ Suspected hyper reactivity.

Clinical trials, concerning the effect of IACS in HOA

The first published data forIACS in HOA are of Hollander J. L. 1951. – observations of 2 patients, injected with 25 mg. Hydrocortisone, who 24 hours after the application have demonstrated a marked improvement of the chief complaints – tenderness and range of motion , staying in the first patient for 7, and in the other for 13 days. Impressed by the result 3 years after Hollander publishes his observations on 77 injectedHJ, in which has been established an improvement, staying for at least 3 days – in 47% of the cases [18].

The next studies describe the methodology of Leveaux V. M. and Quin C.E. from 1956 [19], comparing of the effect of an injection with LA – Procaine in 15 patients to this of Procain + 50 mg Hydrocortisonein other 15 patients.

In the present literature review for the goals of the thesis – „Influence of the bone model on the natural and modified by intra-articular therapies evolution of HOA”, has been performed a systemic search in the data base: Cochrane library/Cochrane CENTRAL; PubMed; Scopus, for the period 1950-24. July 2020. During the search were extracted and analysed the designs of 20 original studies on the application of IACSin HOA for the period 1956-2020 [18-36, 38], as well as 2 published proposals for design of studies,

concerning HOA with the participation of IACSas a therapeutic group [39, 40], 4-descriptive reviews [41, 42, 48, 49], 4-systemic reviews with meta analyses [43-46]and one own meta-analysis [47]. The designs analysis was very helpful to be evaluated the studies quality and the grade of scientific evidence of each of them. It was performed according to the recommendations for evaluation of interventional studies:

For the adequate analysis of the effects of IACS in HOA, concerning the efficacy and effect duration, are included the data from 6 studies [24, 25, 27, 29, 30, 31], highly acknowledged and estimated according to the recommendations for evaluation of interventional studies:

√ Jadad scoring system [52].

√ Cochrane Handbook for Systematic Review-sof Interventions, Version 5.1.0 (updated March 2011). The Cochrane Collaboration. Available from: www.cochranehandbook.org; 2011, [53].

√ TheOxford 2011 Levels of Evidence, Centre for Evidence-Based Medicine, London, UK, 2011, [54].

√ Grading quality of evidence and strength of recommendations, BMJ (Clinical Research edition), [55].

Tables 1 and Table 2 present the characteristics of the studies, used for analysis of the designs and the effect of IACS. The studies used for analysis of the effects of IACS are marked with (¥).

Table 1. Characteristics of the trials, used for analysis of the designs of IACS

Author/Year/ Country	Design/ Quality	Population/ Samples size total/CS/control	Definition of HOA	Therapeutic groups	Arthrocentesis type	Summary: Effects and results Reported adverse effects
Plant et al.,, 1997, UK [22]	DB-RCT (4/IV) CS+LA	Awaiting THR, 45 (OA-27; RA-15; AS-1) ITT-4	ACR + X-Ray changes	Single injection, 4 ml 1% Lidocaine + 80 mg. DM-Upjohn	X-Ray guidance	Median pain score is reduced from 28.5 cm at the base line to 22.4 cm at week 2 and restored the basic values at 26th week.19 patients had 25% improve-mend at week 2, from whom 12 kept this percentage till week 12 and 5 – till week 26.Atrophic models are not appropriate for IACS use. Side effects – no serious side effects were reported.
Flanagan et al., ¥, 1988, UK [20]	DB-RCT (4/III) CS/LA/NS	Awaiting THR, 35 (12/23)	Charnley	Single injection, (1) 0.5% Bpv-10 ml (2) 20 mg TcA+10 ml Bpv (3) 10 ml NS	X-Ray guidance	9/12 in CSgroup,compared to 14/24 in the control group report of a pain improvement at week 4. Statistics is not reported. AE- worsening inCS – high addiction of the patients !
Margules, 2001, USA [23]	Case-Serial trial (5/IV)	Symptomatic HOA, resistance for conventional therapy, could not tolerate surgery 510 – CS only	ACR + X-Ray changes	Single injection, 40mg. TcA.	X-Ray guidance	At week 8 a pain improvement during motion is registered in 189/510 patients. (38.8%) as follows: group with severe changes – K/L III-IV: 9% (21/234); group with mild changes – K/L II-III: 58% (131/226); група с леки промени – K/L II: 90% (46/51). Side effects – not reported.
Kullenberg et al., ¥, 2004, Sweden [24]	DB-RCT (4/III) CS/LA	Awaiting THR, 80 (40/40)	Ahlbäck	Single injection, PB – 2 ml NS + 1%/1 ml (10 mg) Mpv CS – 80 mg TcH	X-Ray guidance	At 3rd week is presented a significant change in the pain at rest and during motion in the CS group, compared to controls.After that VAS values have grown slowly, but because of withdrawal of the control group the results are not taken into consideration Side effects – not reported .
Qvistgaard et al., ¥, 2006, Denmark [25]	DB-RCT (3/II) CS/HA/PBO	Symptomatic HOA, Pain at randomization Total(CS/PB/HA) 101 (32/32/36)	ACR + X-Ray changes	Three injections with 14-day interval: PBO – 2 ml NS CS – 40 mg DM, followed by 2 sham injections HA – 3 x Hyalgan	US-guidance	Effective width of pain reduction during motion is 0.6 (95% CI:0.1-1.1) during the whole period the statistic difference sPBO – CS: P – at week 4 = 0.006, at week 12 P = 0.58. AE-3 patients with transitory facial flushing.
Lambert et al., ¥, 2007, Canada [27]	DB-RCT (3/II) CS/PBO	Symptomatic HOA, at least 6M beforerandomization, resistance for conventional therapy 52 (32/21)	ACR + X-Ray changes	Single injection, PBO – 2 ml NS + 10 mg Bpv, CS – 40 mg TcA + 10 mg Bpv.	X-Ray guidance	OARSIcriteria for response: 22/31 in CS group, compared to 4/12 in the control group at week 8, P < 0.01. AE – one episode of DVT on the 3rd month; 1 from the controls and 3 from the CS group have reported of a transitory increasing of pain.

Contents of table 1

Robinson et al., 2007, UK [28]	Non-R, Non-controlledcohort trial (5/IV) CS/CS	Symptomatic HOA, at least 4M before randomization, 120 Pts (40 mg – 75/80 mg – 45)	X-Ray (K/L) + clinical Dg -WHO	Single injection, 40 mg or 80 mg DM + 3-4 ml 0.5% Bpv	X-Ray guidance	The group with 40 mg has a pain and stiffness improvement,but not and functional improving at week 6, that sustained significant till week 12. The group with 80 mg had a significant improvement of the 3 followed parameters,sustained till week 12. AE – no serious AE.
Micu et al., ¥, 2010, Romania [29]	Case-Control trial (3/IV)	Symptomatic HOA, at least 2M beforee randomization, resistance for conventional therapy 40 Pts/45 HJ	ACR + X-Ray changes (K/L III) + HJ synovitis, defined by the ACR criteria	Single injection, 8 mg Betamethasone + 2 ml Lidocaine 1% + 0.5 ml of air	US-guidance	In control group there was no change in pain score. Lequesneindex (LI) and synovial hypertrophy (SH) on 3rd month. In CS group and on 1st and 3rd month was reported a significant change of pain, which has been highly correlated to the changes of LI.SHis reduced by 75% on the 3rd month, compared to the initial.AE – transitory synovitis after the injection, spontaneously faded for 24-48 hours in 16/45 injected joints.Transitory flush in 16/40 patients.
Spitzer et al., 2010, USA [30]	DB; Randomized prospective without control group [3/III]	Symptomatic HOA 313 (155-CS/150-HA) 305 – ITT	ACR + X-Ray changes (K/L II-III)	Two injection, 2 weeks apart: HA – Hylan G-F 20 CS – 40 mg DM and 1 – sham injection, 2 weeks later	US-guidance	Week 26 – WOMAC-A: HA - ↓16.6mm CS - ↓13.6mm AE – without any serious AE, transitory flush for 24-48 часа, changes of BP and serum glucose for a period of 24-48 hours after the injection.
Atchia et al., ¥, 2011, UK [31]	RCT (3/III) CS/HA/PBO	Awaiting THR, symptomatic HOA, pain at least 1M 77 (19/19/38) ITT-66	ACR + X-Ray –primary, unilateral, K/L grade ≥ III	Single injection, PBO – 3 ml NS; CS – 3 ml/120 mg DM; Duralone (NASHA) 3 ml	US-guidance	OARSI criteria for response 7/19 in CS group, compared to 2/19 in the control group at week 8, P = 0.02. AE – not reported serious AE
Deshmukh et al., 2011, USA [32]	Retrospect. Case-Serial trial (4/IV) CS + LA	Symptomatic HOA at least 4M 217 – CS	ACR + X-Ray changes (K/L)	Single injection, 5 ml 0.5% Bpv + 1 ml/80 mg DM	X-Ray guidance	Pain score reduction at rest and during motion ≥ 50% is accepted as a criterion for a therapeutic response – 148/217 patients at 15 minute after the injection and 155/217 at week 2 – for all the patients. AE – without any serious AE
Young et al., 2012, UK [33]	Randomized Uncontrolled cohort trial (4/IV) CS –LV/HV	Symptomatic HOA, 100 Pts into two group LV-55; HV-55	NA	Single injection, LV – 40 mg TcA + LA – 2 ml 0.5% Bpv HV-additional 6 ml NS	X-Ray guidance	Significant changes in pain on 3rd month: Δ болка: LV: 8.8 (-28%); HV: 8.9 (-28%) AE – transitory facial flush in 1 patient, transitory increase of pain in 2 patients, one episode of hyperglycaemia in DM type I and a regional soft tissue oedema in 1 patient.
Subeddi et al., 2015, UK [34]	Observ. Study (4/IV) CS	Symptomatic HOA, 100/100	ACR + X-Ray changes (K/L)	Single injection, 80 mg DM + 10 ml 0.5% Bpv.	X-Ray guidance	At week 8-82/100 patients are reported as responders for all the grades(K/L)of OA. AE – no SAE reported.
Walter et al., 2019, USA [36]	Retrospect. Case-Serial trial (4/IV) CS + LA	Symptomatic HOA, 113 (56/56) ITT-112	ACR + X-Ray changes (K/L)	Single injection, (1) 40 mg TcA + 3 or 4 ml 0.5% Bpv (2) 80 mg TcA + 3 or 4 ml 0.5% Bpv	X-Ray or US guidance	Non-significant changes in pain at rest and during motion byEuro Quol 5-domain – VAS, as well as for a short time (< 8 weeks): 1 ± 18.32, P = 0.915, as well as for a longer period (> 8 weeks): 0.25 ± 20.58, P = 0.455. AE – NA
Crook et al., 2020 USA [38]	Retrospec. H2H; Non R; No CG; Case-Serial trial (4/IV) CS /CS+HA	Sympt. HOA; 119/119; F-U -36M; Check made at BL; W2; W4; W8; W12; M6; M12; M24; M36	ACR + X-Ray Tonnis 1; 2; 3 = K/L II-III-IV; Pain at walkNRS 10 point HHS AE; HR;	Single injection: CS: TcA Kenalog 40 mg/1 ml; CS+HA: 2 ml/20 mg Supartz® 0.6-1.2 MDa	X-Ray guidance	Significant changes in pain during motion: CS to 7.0 (5-9) decrease to 2.0 (1-3) at W2 (p = 0.0003); CS+HA to 7.0 (5-9) to 2.0 (1-4) atW2 (p = 0.0004). Average duration of significant changes in pain: CS – 6W; HA – 16W (p = 0.0001)

Table 2. Characteristics of the trials, used for analysis of the effect of IACS

Author:	Patients outcomes	Follow-up / Lost to foll/up CS / Contr.	Baseline Values	Weeks 1-4	Week 8	Week 12	More than 12 weeks
Plant et al., 1997 [22]	Pain at walking–VAS; ROM – IR; X-Ray changes at 26 w-k.	26 weeks NA	Pain mediane 28.5 cm ROM-IR:17◦	Week 2: Pain mediane 23.8 cm ROM-IR: 27◦	NA	Week 12: Pain mediane 25.3 cm ROM-IR: 23◦	Week 26: Pain mediane 28.5 cm ROM-IR: 17◦
Flanagan et al., 1998 [20]	Pain at 1-5 NRS	36 weeks Week 4-0/0 Week 8-0/1 Week 24-9/11 Week 36-10/19	NA	Positive responders: week 4 : 9	Positive responders: week 8: 4	NA	Positive responders: week 24: 3 week 36: 2 week 48: 1
Margules, 2001 [23]	Pain at walking –VAS; ROM – IR;	8 weeks NA	NA	NA	Pain relief responders: week 8: severe group: 9% (21/234); moderate group: 58% (131/226); mild group: 90% (46/51)	NA	NA
Kullenberg et al., 2004 [24]	Pain – at rest and weight bearing – VAS; ROM – IR	3(12) weeks Before week 3 0/0 After week 3 0/40 Week 12-40/40	PBO: NA CS: 12.2 ± 2.2	3 weeks: PBO: 12 ± 1; CS: 3.8 ± 2.6 (p < 0.001)	NA	12 weeks : PBO: 12.4 ± 1.8; CS: 7.9 ± 3.9 (p < 0.01)	NA
Qvistgaard et al., 2006 [25]	Pain at rest and walking – VAS; WOMAC; Lequesne;	12 weeks Week 4-2/1 Week 12-6/3	PBO: 42.4 ± 19.17 CS: 44.0 ± 19.17	2 weeks: PBO: 45.52 ± 19.17; CS: 32.38 ± 19.17 (p = 0.006) 4 weeks: PBO: 42.51 ± 19.17; CS : 29.52 ± 19.17 (p = 0.006)	NA	12 weeks: PBO: 38.32 ± 19.17; CS: 35.85 ± 19.17 (p = 0.58)	NA
Lambert et al., 2007 [27]	Pain at walking – WOMAC; Stiffness – WOMAC; Function – WOMAC;	12 weeks Week 8-0/2 Week 12-11/15 Week 24-15/18	PBO: 314.3 ± 76.2 CS: 310.1 ± 54.6	1 month: PBO: 276.4 ± 129; CS: 149.6 ± 113 (p = 0.0005)	2 months: PBO: 306.5 ± 121.2; CS: 157.4 ± 127.2 (p < 0.0001)	NA	NA
Robinson et al., 2007 [28]	Pain – WOMAC-A; Stiffness – WOMAC-B; Function – WOMAC-C	12 weeks NA	40 mg – 12 (2-20) 80 mg – 12 (2-20)	NA	NA	12 weeks: 40 mg – 12 (1-20) (p > 0.05); 80 mg – 10 (1-20) (p = 0.002)	NA
Micu et al., 2010 [29]	Pain at walking – VAS; Lequesne index; Synovial Thickness (ST)	12 weeks NA	Controls: 8.66 ± 0.79 CS: 8.17 ± 0.86	1 month: control: NA CS: 2.77 ± 0.79 (p < 0.001 vs. baseline)	NA	3 months: Control: 7.02 ± 0.53; CS:3.66 ± 0.79 (p < 0.001vs. baseline)	NA
Spitzeret al., 2010 [30]	WOMAC – A; B; C OMERACT-OARSI; ITT (n = 305)	26 weeks Before 26-week: CS – 61: AE-11 Wishes to withdraw-41 Lost to follow-up – 2 Other-7 HA-48: AE-9 W to W-24 L to F-2 Other-13	WOMAC-A: CS 64.53 ± 0.98 HA 63.40 ± 1.0 WOMAC-B: CS 65.06 ± 1.48 HA 66.12 ± 1.52 WOMAC-C: CS 63.03 ± 1.37 HA 64.42 ± 1.4 WOMAC tot: CS 63.26 ± 1.24 HA 64.27 ± 1.27 (P < 0.0001)	Week 4 WOMAC-A: CS-29.49 ± 1.91 HA-17.9 WOMAC-B: CS-26.33 ± 1.83 HA-15.90 ± 1.89 WOMAC-C: CS-26.57 ± 1.73 HA-8.19 ± 1.79 WOMAC-tot; CS-26.98 ± 1.24 HC-18.18 ± 1.75 (P < 0.0001)	NA	NA	Week 26 WOMAC-A: HA-16.6 ± 2.47 CS-19.37 ± 2.48 WOMAC-B: CS-13.70 ± 2.45 HA -15.52 ± 2.47 WOMAC-C: CS-11.53 ± 2.30 HA-13.80 ± 2.32 WOMAC-tot; CS-12.00 ± 2.29 HC-14.70 ± 2.32 (P < 0.0001)

Contents of table 2

Atchia et al., 2011 [31]	Pain at walking – NRS; WOMAC-A; WOMAC-C ITT-66	8 weeks Before week 8 0/0 Week 8-0/1	PB: 6.55 ± 0.68 CS: 5.99 ± 0.62	1 week: PBO: 5.9 ± 0.96; CS:3.06 ± 1.2 (p < 0.001) 4 weeks: PBO: 6.42 ± 1.08; CS: 3.89 ± 1.39 (p = 0.01)	8 weeks: PBO: 6.98 ± 0.89; CS: 5.06 ± 1.23 (p = 0.06)	NA	NA
Deshmukh et al., 2011 [32]	Pain at rest and walking – VAS; 50% reduction in VAS was defined as responders	2 weeks NA	Positive responders – № 150	Positive responders: 15-20 min: 148; Week 2: 155	NA	NA	NA
Younget al., 2012 [33]	Pain at rest and walking – Oxford Pain Chart; OHS WOMAC-A; B; C	12 weeks LV/HV Week 12-0/6	LV-12.2 HV-12.3	NA	NA	3 months: Δ in pain: LV:8.8 (-28%); HV:8.9 (-28%)	NA
Subeddi et al., 2015 [34]	Pain at rest and at walking – OHS – pain score; X-Ray changes at w-k 32 AE – no serious AE	8 weeks NA	NA	NA	Week – 8 Positive responders: 82 (all grades of osteoarthritis)	NA	NA
Walter et al., 2019 [36]	Pain at rest and at walking EuroQuol 5-domain-VAS	24 weeks Before week 24 13	0	NA	< 8 weeks: Δ in EQ5D VAS: 1 ± 18.32 (p = 0.915)	≥ 8 weeks: Δ in EQ5D VAS: 0.25 ± 20.58 (p = 0.455)	NA

Analysis of the trials qualities

From the analysed trials – 5 are randomized, placebo controlled (RCT) [20, 24, 25, 27, 31], in which the randomization is performed regularly with a high probability. 4 of the trials are double blinded (DB-RCT), with a regularly performed blinding at high extent of probability [20, 24, 25, 27]. In addition, [20, 25, 27, 31] report the withdrawn patients, and trials [24, 25, 31] contain ITT (intent to treat) analyses, that increases the quality evaluation. Of the mentioned DB-RCT, one of them [20] is with a great bias – because of the fact that the patients have expected THRand have been informed of that those, who get worse after the injection, will have a priority for the intervention. One RCT [31] – is not double blinded, but only referring to the patients. Despite of this we do not consider that the bias in this trial is higher because only the reported results from the blinded patients are discussed in the final evaluation. Trial 24, after 3rd week reports withdrawal of the whole control group, so the quality of the trial has dropped sharply. In conclusion: trials [25, 27, 31] receive quality evaluation mark 3, respectively trials 20 and 24-4. Concerning the evidence evaluation [52-55], trials [25, 27] are highly evaluated II as well performed RCT, trials [20, 31], receive III, because of the above mentioned reasons.

From the rest of the studies two of them are uncontrolled, cohort trials, [33] – with, [28] – without randomization, comparing the effects of different doses [28] or volumes [33] of IACS, with good blinding, report of AE and withdrawn patients and is scored for the quality and evidence – [28] – 5/IV, a [33] – 4/IV.

Study 29 is a case-control study with a very good quality, concerning the blinding, report of AE and withdrawn patients and ITT analyses and is scored of quality and evidence 3/IV.

The trial of Spitzer et al. [30] is a randomized, DB, cohort, prospective trial of good quality of blinding, report of AE and ITTanalyses, but is without a control group, so its score of quality and evidence is – 3/III.

The rest of the trials: [20] – DB-RCT, in which the weak part are the groups of patients (parallel presence of patients with RA, AS, OA), reducing the quality and evidence score despite of the ITT analyses and report of AE and the withdrawn patients – scores – 4/III.Trials: [23, 32, 36, 38] are case-serial trials, as 3 of them [32, 36, 38] are retrospective and have quality and evidence scores – 4/IV. Trial 34 is an observational of good quality and its evaluation score is – 4/IV. Data are in table 3.

Table 3. Evaluation of the quality of the trials

Author	Randomization	Described randomization is appropriate	Control	Blinding	Blinding method is appropriate	Report of the withdrawn, drop-outs, AE	Total score Jadad / OCEBM 2011-Lv.of Ev.
Plant [22]	Yes	Yes	Yes	Yes	Yes	No	4/IV
Flanagan [20]	Yes	NA	Yes	Yes	Yes	Yes	4/III
Margules [23]	No	No	No	No	No	Yes	5/IV
Kullenberg [24]	Yes	Yes	Yes	Yes	Yes	Yes;AE – no	4/III
Qvistgaard [25]	Yes	NA	Yes	Yes	Yes	Yes	3/II
Lambert [27]	Yes	Yes	Yes	Yes	Yes	Yes	3/II
Robinson [28]	No	No	No	Patients	Yes	Yes	5/IV
Micu [29]	No	No	Yes	No	No	Yes	3/IV
Spitzer [30]	Yes	Yes	No	Yes	Yes	Yes	3/III
Atchia [31]	Yes	Yes	Yes	Patients	NA	Yes	3/III
Deshmukh [32]	No	No	No	No	No	Yes	4/IV
Young [33]	Yes	Yes	No	Yes	Yes	Yes	4/IV
Subeddi [34]	No	No	No	No	No	Yes	4/IV
Walter [36]	No	No	No	No	No	Yes	4/IV

On the basis of the quality and evidence scores of the discussed trials, for analysis of IACS effects were selected 5 trials with scores 3/II; 3/III; 3/IV or 4/III: [24, 25, 27, 29, 31].

The first and basic object of interest in the analysis was the reported pain by the patients. We used the data with the highest pain score for each of the included in the analysis trials,for the longest accessible period of follow-up – according to the hierarchical method of според Jüni et al. [56].

Taking into consideration the great heterogenity between the trials – with different follow-up periods and different basic levels of pain score as a basic index – was chosen the model of Mantel-Haenszel, based on the default fixed effects, that is considered as the most stable in cases of effects' heterogenity.

There were created standard mean deviations (SMDs), comparing the mean deviations in each result for pain between the active and control group – at each moment during follow-up. In absence of results of any difference in deviations between the active and control groups and inability for answer of the corresponding author was implemented so called mean standard deviation – mSD = [SD (baseline-follow-up)], It is formed by combining of SD calculated at the entrance and during follow-ups with calculated correlation between the exit and the following visits from 0.5, analysing sensitivity, using of a correlation 0.25 и 0.75 with the help of the following formula (Figure 1), according to recommendations of Cochrane Collaboration Centre [53].

Combined results in the different groups, presented as SMD are shown on Fig. 1.

IACS effects upon the pain: speed – onset, grade and duration:

√ *Onset* – the most rapid effect is demonstrated in the trial of Deshmukh et al. [32]. Hereby, 20 min. after the manipulation 148/217 (68.2%) have a positive answer, defined as ≥ 50% pain reduction. 2 weeks later the positive answer grew up to 155/217 (71.4). Atchia et al. [31] in the results at week1 report for SMD of 1.5 (NRS) and 1.9 (WOMAC-A) for "worst" pain. All these makes us consider that the initial peak effect of IACS is between 2-7 days.

√ *Magnitude of effect and temporal dynamics* – IACS effectis initially high (above mentioned data of Atchia et al.), but with a tendency to reduce during time. All the trials, presenting results from week 2 [22, 25, 30, 31, 32] and week 3 [24], report of significant differences from the exit values [22, 24, 25, 30, 31, 32] and/or between the therapeutic and control group [24; 25]. As the data of Atchia et al. [31], so the data from the other authors – Qvistgaard et al. [25]; Spitzer et al. [30] the comparisons of the first

$$SD_{(baseline-follow\text{-}up)} = \sqrt{SD^2_{baseline} + SD^2_{follow\text{-}up} - \left(2 \times Cor_{(baseline,follow\text{-}up)}\right) \times SD_{baseline} \times SD_{follow\text{-}up}}$$

Fig. 1. Use of calculation of mSD formula [53]

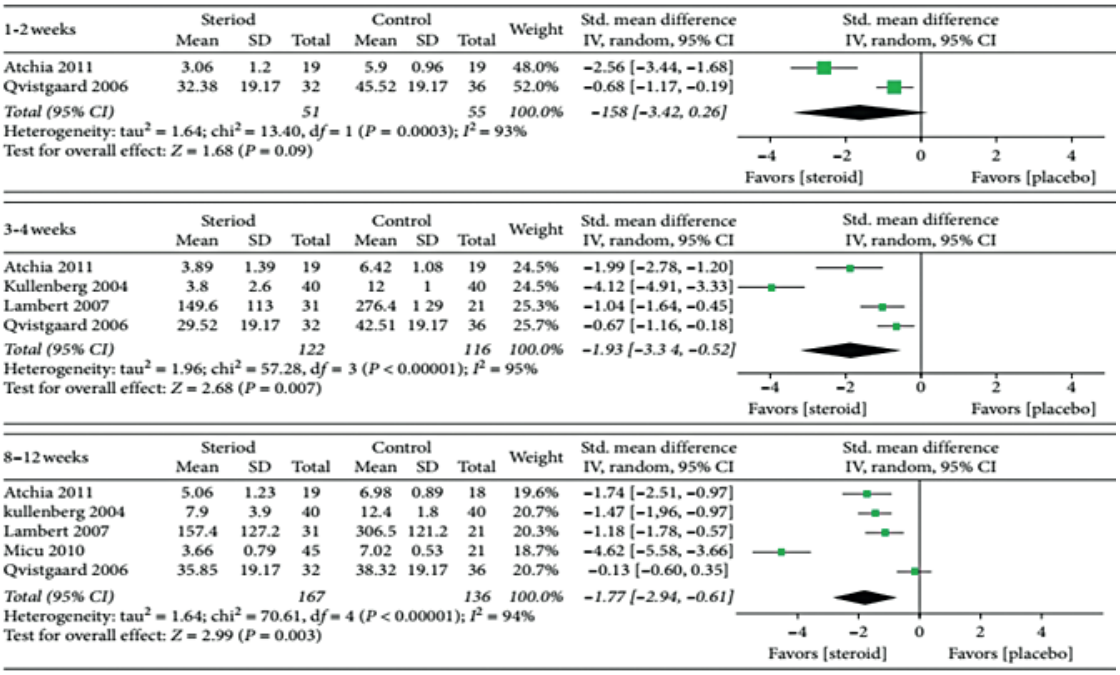

Fig. 2. Forest plots – for pain during different periods of time [53]

controls (1-3 week) to the following,reveal of a drop of the magnitude of the effect: Atchia et al.[31] 1.5/1.9 – 1.0/1.1 at week 8; Qvistgaard et al. [25] 32.38 ± 19.7 (p = 0.006) / 29.52 ± 19.7 (p=0.006). Only one trial Lambert et al. [27] supposes a sustained effectiveness without any significant difference 1-2 month. This fact is explained by the use of CS (TcA), a drug form that is staying for the longest period in the joints, as well as because the interval between the visits was only 1 month.

√ *Maximal duration of the effect* – data for a sustaining till 12 weeks' effect of IACSare presented in trials: 20, 22, 25, 28, 29, 30, 33. In the trial of Flanagan et al. [20], despite of the mentioned high bias and the author's conclusion of a bad IACS effect, there are objective data that 75% of the patients had a significant reduction of pain score on 1st month, and 33% of them kept this positive response on 3rd month. Plant et al. [22] report of a reduction of pain median from 28. 5cm.atbaseline, to 23.8 cm – atweek – 2 and – 25.3 cm, at week 12, 19/45 patients had a significant improvement ≥ 25% for pain median. 12 of them kept this percentage till week 12, and 5 – till week 26. The data on 3rd month from the trial of Kullenberg et al. [24] were not reported due to the withdrawal of the control group from the trial after week 3. In Robinson et al. [28], the high dose of 80mg has kept the significant deviations in the three components of WOMAC scale: A; B и C – at week 12. The data of Qvistgaard et al. [25], show a significant pain reduction during motion in all of the monitored sites (2/4/12 week) with generally mild therapeutic effect range (SMD) from 0.6 (95% CI: 0.1-1.1). Micu et al. [29] report significant deviation of pain during motion and Lequesne index on 1stmonth (2.77 ± 0.79; p < 0.001), kept the same on 3rd month (3.66 ± 0.79; p<0.001), compared to controls (7.02 ± 0.53). Forest plot analysis for week 12, however shows deviations these data from the values reported in the other trials. This deviation is probably due to the absent randomization in the trial of Micu et al. [29].

Despite some of the trials [20, 22, 30] report data of an effect after 12th week: Plant et al. [20] –definite return of the pain median to the basic at week 26, Flanagan et al. [22] – presence of 3-responders at week 26, Spitzer et al. [30] – sustained pain reduction (WOMAC-A) at week 26 with 13.6 mm, compared to the basic values in IACS group, these trials are of low quality and evidence score – [30] without a control group, [20] consisted of patients with OA and inflammatory joint diseases at one and the same time, [22] – with a high bias, and we have no reasons to accept a longer staying effect.

Effect upon the function – the second issue of interest in the review were the effects of IACS upon the functional capacity of the patients. From the 4 trials, using subjective methods for functional assessment, 3 reveal a significant improvement in the functional capacity compared to base line and

also when compared to the control group [25, 27, 31], including a significant improvement of modified Katz ADLindex at 3rd week [24], WOMAC-C subscale [25, 27, 31], WOMAC-C + SF-36 [27] – at week 8. Atchia et al. [31], report of the magnitude and duration of the effect of IACS upon the function (based on the deviations in WOMAC-C subscale), reflecting to a great extent pain score deviations: at week 1, SMD is high – to 1.3, drops to 0.9 at week 4 and to 0.4 at 8th week. In the trial of Lambert et al. [27], analogous of the effect upon the pain, the functional improvement has no significant reduction between 1st and 3rd month. Several trials [22, 23, 24, 27] use ROM-IR, as an objective evaluation index for hip joint function, but with controversial results. The trial of Kullenberg et al. [24], reveals a significant improvement of ROM-IRat 3rd week in IACS group, compared to the base line values and also to the control group. In the trial of Plant et al. [22], the internal rotation has significantly increased from 17◦ до 27º at 2nd week, after that returns to 23º at week 12. In the trial of Margules [23], none of the patients with a severe form (K/L-III-IV) has notbeen improved, referring to ROM-IR; in the group with a mild form (K/L-II-III), 48% from the patients had an increase of ROM-IRby at least 10º, sustained till week 8, in the group with a light form (K/L-II), 90% of the patients had an increase by at least 10º, sustained till 8th week. Several trials [22, 25, 28, 29], report significant functional changes, sustained till week 12, that gives the opportunity to conclude that the magnitude and duration of the effect of IACS upon the function reflect the pain score deviations with minimal quantitative variations.

Dependences of IACS effect

√ *Dose and medication* – the dose effect upon the magnitude and duration of IACS effect is discussed in the trial of Robinson et al. [28]. The authors use 2 doses: 40 mg и 80 mg MP – (Depo Medrone-Upjohn) + LA 4 ml 0.5% Bpv. in 120 patients – 75 with 40 mg and 45 with 80 mg Both groups report reduction of pain and stiffness (WOMAC-A; B) at week 6: 40 mg reduction of pain score from 12 – at base line, to 10 ($p < 0.001$); 80 mg – reduction of pain score from12 – at base line, to 8 ($p < 0.001$). However, only the group with 80 mg, registers significant functional improvement (WOMAC-C) – at week 6, which improvements (pain, stiffness function) are sustained significant at week 12 (pain – from 12, at base line to 10; $p = 0.002$). Another trial of Walter et al. [36], in 113 patients (56/56) are testing the effect of 2 doses of TcA: 40 mg and 80 mg + LA – 4 ml 0.5% Bpv., the analyses (Fisher test)show an absence of significant associations between the patients with different doses of TcA ($P = 0.818$).One of the possible explanations is that Robinson et al. use MP – IACS, that is staying in the joints for the shortest period, in which the higher dose interfere in a longer and more powerful effect, while Walter et al. use TcA – the longest staying in joint cavity CS, in which the persistent dose of 40mg is completely sufficient for the achievement of the total CS effect, that is why the dose of 80 mg has no marked advantages.

√ *Radiographic stage and model* – the impact of radiographic model is discussible only in the trials of Plant et al [22] and Flanagan et al. [20]. The authors conclude that atrophic models do not respond to therapy, respectively IACS are of no use, which can be explained either by the absence of an inflammatory process (its low activity in these models) or, that IACS change unfavorably the bone remodeling. Differently, the impact of the radiographic stage (K/L), is discussed in several studies with controversial conclusions:

a) more advanced damages respond worse – Margules [23] in his analysis of 510 cases, classified according the radiographic stage (K/L) in: severe-K/L III-IV; mild – K/L-II-III and light -K/L-II all of them injected with 40 mg TcA, the categorical conclusion is that the lighter cases respond positive in a higher percentage: severe 21/234 – 9%, mild 131/236 – 48%, light 46/51 – 90%.

b) more advanced damages respond better – Deshmukh et al. [32], in a retrospective analysis of a series of 217 cases, classified in 4 groups according to the radiographic class (K/L), injected with one and the same combination 80 mg MP+LA 5 ml 0.5% Bpv. At week 2 the positive responders (reduction of pain at rest and during motion ≥ 50% from base line) were 155/217, for all radiographic stages, as the more severe cases have tendency to respond with a more significant reduction.

c) the grade of pain reduction after IACS is independent of the severity of damages – Subeddi et al. [34], in an observational trial on 100 patients, splitted in 4 groups, according to radiographic class (K/L) and injected with 80mg.DM + LA – 10 ml 0.5% – at week 8, 82/100 – 82% of patients report of significant improvement of pain score, compared to base line ($p < 0.01$), but not associated to the radiographic class of HOA ($p = 0.51$).The authors: Qvistgaard et al. [25]; Lambert et al. [27] and Robinson et al. [28], also mention that the degree of pain score reduction after IACS has been independent the class (K/L) of OA, despite they do not report any data in their re-

sults. From the above mentioned results only those of Deshmukh et al. [32], were statistically significant.

However, should not be underestimated the fact that despite they look similar at first glance, different issues are concerned: percentage of responders of the different radiographic stages and magnitude of the effect – Margules comments % of responders, i.e. the advanced damages are associated with a lower percent of a positive response. While Subeddi et al. [34] and Deshmukh et al. [32] comment the magnitude of effect – there is no difference in the grade of pain reduction in the different stages. Qvistgaard et al. [25], Lambert et al. [27] and Robinson et al. [28] also discuss the magnitude of the effect, but the data are not presented. In summary we can say that the grade of morphologic damage (K/L grade) is in a negative association with % of responding to IACS patients and not associated with the magnitude of response.

The presence of synovitis and effusion – commented in the trials of: Micu et al. [29], Atchia et al. [31] and Qvistgaard et al. [25]. Differently from Micu et al. [29], where synovitis is an inclusion criterion, it was present in 100 % of the patients' despite of its different extent of manifestation, in the trials of Qvistgaard et al. [25] and Atchia et al. [31], synovitis was an occasional finding with incidence 21% [25] and 26% [31]. Both trials [25, 31], report of a good response to IACS in the presence of synovitis while Qvistgaard et al.stop at this point + the remark that the group with HA gives a bad response when synovitis is present, in Atchia et al. [31], practically in the group of IACS, consisting of 19 patients: 10 from the 14 responders at week – 1, 10 from the 11 responders at week – 4 and 7, from the 7 responders at week 8, were with synovitis at base line and no one without synovitis had a positive response at week 8. The natural conclusion is that the synovitis is the only criterion, predicting a positive response to IACS (Fisher's exact test between number of responders, week 4 and 8; P = 0.04). In the trial of Micu et al. [29], the exit values on 1st and 3rd month concerning pain reduction in the subgroups with variably manifested synovitis were equal, i.e. the severity of the synovitis is not a predictive factor for the magnitude of the effect of IACS.

√ *Similar to the facts of the impact* of K/L class and here different issues are concerned: in Achia et al. [31] – the % of responders at week 8 in presence of synovitis, while in Micu et al. [29] – a lack of correlation between the synovitis severity and the magnitude of the effect of IACS. So, the presence of synovitis is a predictor of a more frequent response, while its severity does not influence the magnitude of effect. This conclusion is radically different from that in the reviews of Zhong et al 2020 [45]; M. Choueiri et al 2020 [42].

√ *The injected volume, sex, age, BMI* etc. The injected volume potentially could exert an impact on the effect of IACS, based on lavage and the increased distribution of the active substance in synovium. On this basis Young et al [33], perform a trial, testing the effect of 40 mg/1 ml TcA + LA-2 ml 0.5% Bpv (3,0 ml total volume) as a group of low volume (LV), vs a group with added 6.0 ml NS, as a group of high volume (9.0 ml total volume). Both groups demonstrate a significant effect on 3rd month, compared to base line ($p < 0.001$), but do not present a statistically significant variation in the percent of responders or the magnitude of the effect between the injected different volumes ($p = 0.95$). Having in mind the similar effectiveness the authors recommend the use of volumes between 3 and 9 ml in the studies on intraarticular therapies for HJ. Regarding the factors age, sex, BMI none of the analysed studies report of established correlations with the percent of responders or the magnitude of the effect of IACS.

Conclusion

Variability of the results of HOA IACS therapy is due from one side to the influence of IACS on number of pain characteristics as onset, magnitude, temporal dynamics, maximal duration of the effectual, also upon the function, and from the other side – the dependence of IACS effect of dose and medication, radiographic stage and model, the presence of synovitis and effusion, the injected volume etc.

Библиография / References

1. Lavelle W, Lavelle ED, Lavelle L. Intra-articular injections. Anesthesiology Clinics, 2007,25(4), 853-862. http://doi.org/10.1016/j.anclin.2007.07.002.
2. Gossec L, Dougados M. Intraarticular treatments in osteoarthritis: from the symptomatic to the structure modifying. Ann Rheum Dis, 2004, 63(5),478-482.
3. Dobson MM. A Check on the Anatomical Accuracy of Intra-Articular Hip Injections in Relation to the Therapy of Coxarthritis. Ann Rheum Dis, 1948, 7(3), 172-174.
4. Dobson MM. A Further Anatomical Check on the Accuracy of Intra-Articular Hip Injections in Relation to the Therapy of Coxarthritis. Ann Rheum Dis, 1950,9(3), 237-240.
5. Landsmeer JMF, Koumans AKJ. Anatomical Consideration in Injection of the Hip Joint. Ann Rheum Dis, 1954, 13(3), 246-249.
6. Leopold SS, Battista V, Oliverio JA. Safety and efficacy of intraarticular hip injection using anatomic landmarks. Clin Or-

thop Relat Res, 2001(391),192-197. doi: 10.1097/00003086-200110000-00021.
7. Mauffrey C, Pobbathy. Hip Joint Injection Technique Using Anatomic Landmarks: Are we accurate?A Prospective Study. The Int. J Orthopedic Surg, 2006, 3(1), 1-4.
8. Sapundzhiev L, Sapundzhieva T. Batalov A et al. Study on Accuracy of Blind and Ultrasound guided Arthrocentesis of Hip joint. J Rheum Dis 2020, 6(2) DOI: 10.23937/2469-5726/1510081.
9. Jordan KM et al. EULAR Recommendations 2003: an evidence based approach to the management of knee osteoarthritis: Report of a Task Force of the Standing Committee for International Clinical Studies Including Therapeutic Trials (ESCISIT). Ann Rheum Dis, 2003,62(12), 1145-1155.
10. Diracoglu D et al. Knee vs hip single – joint intraartcular hyaluronic acid injection in patients with both hip and knee osteoarthritis: a pilot study. Clin Rheumatol, 2009, 28, 1021-1024. DOI 10.1007/s10067-009-1199-7.
11. Zhang W et al. OARSI recommendations for the management of hip and knee osteoarthritis, Part II: OARSI evidence-based, expert consensus guidelines. Osteoarthritis Cartilage, 2008,16(2), 137-162.
12. Zhang W et al. EULAR evidence based recommendations for the management of hip osteoarthritis: report of a task force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). Ann Rheum Dis, 2005, 64(5), 669-681.
13. Hochberg MC et al. American College of Rheumatology 2012 recommendations for the use of non pharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. Arthritis Care Res (Hoboken), 2012, 64(4), 465-474.
14. Banuru RR et al. OARSI guidelines for non-surgical management of knee, hip and polyarticular osteoarthritis. Osteoarthritis Cartilage, 2019, 27(11), 1578-1589.
15. Shirley PChYu et al. Predictors of placebo response to local (intra-articular) therapy in osteoarthritis: an individual patient data meta-analysis protocol. BMJ Open, 2019, 9(5), e027372. doi:10.1136/bmjopen-2018-027372.
16. Altman RD et al. Clinical benefit of intraarticular saline as a comparator in clinical trials of knee osteoarthritis treatments: A systematic review and meta-analysis of randomized trials. Semin Arth Rheum, 2016,46(2), 151-159.
17. Zhang W et al. The placebo effect and its determinants in osteoart-hritis: meta-analysis of randomized controlled trials. Ann Rheum Dis, 2008, 67(12), 1716-1723.
18. Hollander JL. Intra-Articular Hydrocortisone in Arthritis and Allied Conditions, A Summary of Two Years‘ Clinical Experience. J Bone Joint Surg., 1953, 35A, 983-990.
19. Leveaux VM, Quin CE. Local injection of hydrocortisone and procaine in osteoarthritis of the hip joint. Ann Rheum Dis, 1956,15(4), 330-337.
20. Flanagan J et al. Intraarticular injection for pain relief in patients awaiting hip replacement. Annals of the Royal College of Surgeons of England, 1988,70(3), 156-157.
21. Sparling M et al. Radiographic follow-up of joints injected with triamcinolone hexa-cetonide for the management of childhood arthritis. Arthritis Rheum, 1990,33(6), 821-826.
22. Plant MJ et al. Radiographic patterns and response to corticosteroid hip injection. Ann Rheum Dis, 1997, 56(8), 476-480.
23. Margules KR. Fluoroscopically directed steroid instillation in the treatment of hip osteo-arthritis:safety and efficacy in 510 cases. Arthritis & Rheum, 2001,44(10), 2449-2450.
24. Kullenberg B et al. Intra-articular corticosteroid injection: pain relief in osteoarthritis of the hip? J Rheumatol, 2004,31(11), 2265-2268.
25. Qvistgaard E et al. Intra-articular treatment of hip osteoarthritis: a randomized trial of hyaluronic acid, corticosteroid, and isotonic saline. Osteoarthritis and Cartilage, 2006, 14(2), 163-170.
26. Shah NH et al. Intra articular corticosteroid hip injections: a review of 63 consecutive patients. Eur J Orthop Surg Traumatol, 2006, 16(1), 20-23.
27. Lambert RGW et al. Steroid injection for osteoarthritis of the hip: A randomized, double-blind, placebo-controlled trial. Arthritis Rheum, 2007, 56(7), 2278-2287.
28. Robinson P, Keenan A M, Conaghan PG. Clinical effectiveness and dose response of image-guided intra-articular corticosteroid injection for hip osteoarthritis. Rheumatology (Oxford), 2007, 46(2), 285-291.
29. Micu MC, Bogdan GD, Fodor D. Steroid injection for hip osteoarthritis: efficacy under ultrasound guidance. Rheumatology, 2010,49(8), 1490-1494.
30. Spitzer AI et al. Hylan G-F 20 improves hip osteoarthritis: a prospective, randomized study. Phys Sportsmed, 2010, 38(2), 35-47.
31. Atchia I et al. Efficacy of a single ultrasound-guided injection for the treatment of hip osteoarthritis. Ann Rheum Dis, 2011,70(1), 110-116.
32. Deshmukh AJ et al. Intra-articular hip injection: does pain relief correlate with radiographic severity of osteoarthritis? Skeletal Radiol, 2011,40(11), 1449-1454.
33. Young R et al. Therapeutic hip injections: is the injection volume important? Clin Radiol, 2012, 67(1), 55-60.
34. Subedi N et al. Effectiveness of fluoroscopy-guided intra-articular steroid injection for hip osteoarthritis. Clin Radiol, 2015, 70(11), 1276-1280.
35. Araujo JP et al. Pain reduction and improvement of function following ultrasound-guided intraarticular injections of triamcinolone hexacetonide and hyaluronic acid in hip osteoarthritis. J Biol Regul Homeost Agents, 2016, 30(4),51-62.
36. Walter WR et al. Clinical and patient-reported outcomes after image-guided intra-articular therapeutic hip injections for osteoarthritis-related hip pain: a retrospective study. Skeletal Radiology, 2019,48(5), 713-719.
37. Creamer P. Intra-articular corticosteroid injection in osteoarthritis: do they worn and if so, how? Ann Rheum Dis, 1997, 56(11), 634-636.
38. Crook P et al. Efficacy of intra-articular Hyaluronic acid and Cortisone Compared to Cortisone alone for symptomatic Hip Osteoarthritis. J Arthritis, 2020,8(1), 1000278. Doi:10.4172/2167-7921.1000278.
39. Paskins Z et al. A randomized controlled trial of the clinical and cost-effectiveness of ultrasound-guided intra-articular corticosteroid and local anaesthetic injections: the hip injection trial (HIT) protocol. BMC Musculoskelet Disord, 2018, 19(1), 218. doi: 10.1186/s12891-018-2153-0
40. Colen S et al. Comparison of intra-articular injections of hyaluronic acid and corticosteroid in the treatment of osteoarthritis of the hip in comparison with intra-articular injections of bupivacaine. Design of a prospective, randomized, controlled study with blinding of the patients and outcome assessors. BMC Musculoskelet Disord, 2010,11, 264. www.biomedcentral.com/1471-2474/11/264.
41. Kruse D. Intraarticular cortisone injection for osteoarthritis of the hip. Is it effective? Is it safe? Curr Rev Musculoskelet

Med, 2008,1,(3-4), 227-233. Narrative review. doi: 10.1007/s12178-008-9029-0
42. Choueiri M, Chevalier X, Eymard F. Intraarticular Corticosteroids for Hip Osteoarthritis: A Review. Cartilage, 1-10, DOI:10.1177/1947603520951634-2020.
43. Hirsch G, Kitas G, Klocke R. Intra-articular corticosteroid injection in osteoarthritis of the knee and hip: factors predicting pain relief. A systematic review. Semin Arth Rheum, 2013, 42(5), 451-473.
44. McCabe PS et al. The efficacy of intra-articular steroids in hip osteoarthritis: a systematic review. Osteoarthritis Cartilage, 2016, 24(9), 1509-1517.
45. Zhong HM et al. Intra-Articular Steroid Injection for Patients with Hip Osteoarthritis: A Systematic Review and Meta-Analysis. Hindawi, BioMed Research International, Volume 2020, Article ID 6320154, 12 pages, https://doi.org/10.1155/2020/6320154
46. Bowens A. The effectiveness of injection of steroid to the hip as a form of intervention-nal pain management: A Systematic review-2018; International Centre for Allied Health Evidence, School of Health Sciences, City East Campus, University of South Australia, Adelaide, South Australia 5000, Website: www.unisa.edu.au/cahe
47. Van Middelkoop M et al. -e OA trial bank: meta-analysis of individual patient data from knee and hip osteoarthritis trials show that patients with severe pain exhibit greater benefit from intra-articular glucocorticoids. Osteoarthritis and Cartilage, 2016, 24(7), 1143-1152. Doi:10.1016/j.joca.2016.01.983.
48. Kaspar J et al. Intra-articular steroid hip injection for osteoarthritis: a survey of orthopedic surgeon in Ontario. Can J Surg, 2005, 48(6), 461-469.
49. Pekarek B et al. Intra-articular corticosteroid injections: a critical literature review with up-to date findings. Foot (Edinb), 2011,21(2), 66-70.
50. Hess S et al. Association of rapidly destructive osteoarthritis of the hip with intra-articular steroid injections. Arthroplast Today, 2018, 4(2), 205-209.
51. Charalambous CP, Prodromidis AD, Kwaees TA. Do intraarticular steroid injections increase infection rates in subsequent arthroplasty? A systematic review and meta-analysis of comparative studies. J Arthroplasty, 2014, 29(11), 2175-2180.
52. Jadad AR et al. Assessing the Quality of Reports of Randomised Clinical Trials: Is blinding Necessary? Control Clin Trials, 1996, 17(1), 1-12.
53. Higgins JPT, Green S. Cochrane Handbook for Systematic Reviews of Interventions. Version 5.1.0 (updated March 2011).The Cochrane Collaboration. Available from: www.cochranehandbook.org; 2011.
54. Howick J et al. OCEMB Oxford 2011Levels of Evidence, Centre for Evidence-Based Medicine, London, UK, 2011.
55. Atkins D et al. Grading quality of evidence and strength of recommendations. BMJ, 2004,328(7454), 1490. doi: 10.1136/bmj.328.7454.1490
56. Jüni P, Reichenbach S, Dieppe P. Osteoarthritis: rational approach to treating the individual. Best Pract Res Clin Rheumatol, 2006,20(4), 721-740.

Постъпил за печат: 18.11.2020 г.

Submitted: 18.11.2020

✉ *Адрес за кореспонденция:*
Д-р Любомир Сапунджиев
Медицински факултет
Катедра по пропедевтика на вътрешните болести
МУ – Пловдив
Пловдив, България
e-mail: sapoundjiev@abv.bg

✉ *Correspondence address:*
Lyubomir Sapundjiev, MD
Medicine Faculty
Department of Propedeutic of Internal Diseases
MU – Plovdiv
Plovdiv, Bulgaria
e-mail: sapoundjiev@abv.bg