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REVIEW ARTICLES

Safety of intra-articular glucocorticoid injections – state of the art

Duarte-Monteiro AM[1], Dourado E[1], Fonseca JE[1], Saraiva F[1]

ABSTRACT

Intra-articular glucocorticoid injection (IAGCI) is frequently used to treat joint pain and inflammation. While its efficacy has been extensively studied, there are not as many detailed descriptions regarding safety. This review aimed to describe the immediate-, short- and long-term complications of IAGCI and their predictors.

Most studies mainly report mild and self-limited adverse events with an incidence similar to placebo. However, the reported incidences vary significantly and are mostly inferred from retrospective data. Septic arthritis is the most feared adverse event due to its association with high mortality. Other short-term local complications include injection site pain, post-injection flare, skin hypopigmentation and atrophy, and tendon rupture. Systemic side effects are common, including vasovagal reactions, flushing, increased appetite and mood changes, hyperglycemia in diabetic patients, and bleeding in high-risk patients.

Few predictors of complications have been systematically evaluated. However, male gender, advanced age, and pre-existing joint disease have been suggested in retrospective studies to correlate with infection risk.

Overall, in most studies, only severe adverse event rates are reported, with no systematic prospective evaluations of safety and no report of predictors of complications. Therefore, since IAGCI is a routinely used treatment, more detailed knowledge of adverse events and complications is warranted.

Keywords: Intra-articular agents; Synovium; Ultrasonography; Pain assessment and management; Osteoarthritis.

INTRODUCTION

Several intra-articular therapies (IATs) were developed and explored by rheumatologists to improve patients' outcomes, including pain and function. Of these, intra-articular glucocorticoid injections (IAGCI) are the most extensively performed for the local treatment of synovitis, hydrarthrosis and joint pain, regardless of its' primary cause[1–5]. The first use of oral cortisone in rheumatic diseases dates back to 1949, and intraarticular use followed not too long after, in 1951[6].

IAGCI aims to improve joint outcomes through a local anti-inflammatory effect, especially when inflammation occurs in an isolated joint. Regarding this routinely used treatment that has been around for seven decades, how can we today answer our patients' questions, such as "Is it safe?", "Will it hurt?" or "Are there any severe risks?".

[1] Rheumatology Department, Centro Hospitalar Universitário Lisboa Norte (CHULN), Centro Académico de Medicina de Lisboa (CAML), Lisbon, Portugal

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Correspondence to: Ana Margarida Duarte Monteiro
E-mail: amdm@campus.ul.pt

METHODS

In order to try to answer some of these questions, we performed a narrative review of the literature. The Pubmed and Cochrane Library databases were searched using the keywords "intra-articular glucocorticoids", "intra-articular steroids", "intra-articular glucocorticoid injections", "intra-articular steroid injections", "intra-articular injection safety" and "synoviorthesis safety". We included RCTs, non-randomised trials, systematic reviews and narrative reviews published up to December 2022 that mentioned safety data regarding IAGCI. The reviews references were also screened for additional studies. All papers unrelated to the scope of this review were excluded.

BRIEF REPORT ON THE EFFICACY OF IAGCI

Osteoarthritis

There are conflicting reports regarding IAGCI efficacy, especially long-term. Studies have previously documented short-term pain relief in knee osteoarthritis (OA) patients[7]. However, a meta-analysis designed to determine the benefits and harms of IAGCI compared

with a sham injection or no treatment in patients with knee OA (including trials with a follow-up time of up to 26 weeks) found that the quality of the available evidence was overall low[8]. However, the available data suggested that IAGCI have some benefits in pain and function up to 13 weeks after the procedure[8].

IAGCI effectively reduce pain and improve hand function in patients with trapeziometacarpal (TMC) joint OA (rhizarthrosis)[2]. The combination with hyaluronic acid (HA) is also a therapeutic option, and it has recently been shown that the injection of HA and steroids in patients with TMC joint OA leads to improve during activity when compared to the injection of steroid alone at 3 months[9]. IAGCI also seems useful in hip OA[10], reducing pain up to 12 weeks after the procedure and improving range of motion[11], and in acromioclavicular joint OA, in which US-guided IAGCI alleviated symptoms and improved functional status in a 6-month follow-up in a retrospective study[12].

Predictors of response to IAGCI have been described, although the evidence is inconsistent[13]. Higher baseline radiographic severity of OA, such as greater joint space narrowing and higher Kellgren-Lawrence grade, seem to be associated with reduced long-term response[14–16]. Surprisingly, synovitis or hydrarthrosis do not predict response to IAGCI[14].

Inflammatory arthropathies

Regarding inflammatory arthropathies, IAGCI also have a recognised role in the therapeutic strategies not only for rheumatoid arthritis (RA) but also for juvenile idiopathic arthritis (JIA) and spondyloarthropathies, including psoriatic arthritis.

Ultrasound (US)-guided intra-articular triamcinolone acetonide injection can be effective in refractory small joints arthritis in RA patients, with improvements in visual analogue scale (VAS) for pain and tenderness up to 12 weeks[4].

Unguided sacroiliac injections for refractory sacroiliac pain due to spondyloarthropathies have also shown significant improvement in pain (patient-reported and elicited by the clinicians' sacroiliac examination) that was maintained through week 2017. Additionally, a prospective study including 220 psoriatic arthritis patients submitted to IAGCI concluded the procedure was effective, as defined by no tenderness or effusion in the injected joints (including wrist, finger joints, and knee) at three months[18].

IAGCI has also proven effective in oligo-articular juvenile idiopathic arthritis (JIA), with some reports suggesting differences between glucocorticoids, favouring triamcinolone hexacetonide over triamcinolone acetonide[19].

Choosing the right glucocorticoid

It is also important to note that there is limited data comparing the efficacy of different glucocorticoids. Some data favour the use of a long-acting crystalline form of glucocorticoids, such as triamcinolone hexacetonide or methylprednisolone acetate, because these crystals persist longer in the synovial fluid[20]. A systematic review of randomised controlled trials (RCTs), including intra-articular and peri-articular injection RCTs in patients with peri-arthritis, OA or RA, showed that triamcinolone hexacetonide is superior to triamcinolone acetonide, methylprednisolone and betamethasone[21].

Regarding safety, comparative data is even more limited. Triamcinolone acetonide is the most frequently used glucocorticoid in either efficacy or safety evaluation studies, so most data pertains to this specific compound.

SAFETY OF IAGCI: DO WE KNOW ENOUGH?

While some questions can still arise regarding the efficacy of this procedure, it has nonetheless been extensively studied. However, there are not as many detailed and systematic descriptions of possible immediate-, short- and long-term adverse events or their predictors. There are also no studies comparing the rate and type of adverse events considering the type of joint disease (degenerative *vs* inflammatory) leading to the procedure.

Safety data – a first look

Our review of the available literature shows that IAGCI seems to be overall safe, with a reported incidence of adverse events similar to placebo[8,22–24], including mostly mild and self-limited adverse events.

A recent overview of systematic reviews concluded that IAGCI behaves similarly to placebo concerning safety outcomes in knee and hip OA, shoulder capsulitis, or RA[22].Additionally, there were no differences between different IAGCI compounds and doses[22]. However, only systematic reviews of RCTs were included in this overview, and no firm conclusions could be drawn for inflammatory arthritis due to limited data[22]. Worryingly, not all RCTs of IAGCI included safety data, and safety reports consisted mainly of the frequency of adverse events, with no further analysis, specifically regarding predictors of the adverse events

An RCT that included 160 patients with early RA showed that performing IAGCI for refractory synovitis as a part of a treat-to-target approach seems safe, regardless of the treated joint. In this study, intra-articular injections of betamethasone were administered in small and large peripheral joints (including shoulders, elbows, wrists, metacarpophalangeal, proximal interphalangeal, knees, ankles and metatarsophalangeal). These IAGCI effectively treated synovitis, and no significant adverse events were reported[25]. A double-blind,

randomized comparative study of triamcinolone hexacetonide and dexamethasone intra-articular injection for the treatment of knee joint arthritis in RA also attested for the safety of the procedure, with no recorded treatment complicationsNo differences were found regarding efficacy or safety when comparing the two compounds[26].

A 2015 Cochrane review aiming to determine the benefits and harms of IAGCI compared to sham or no intervention in knee OA included 27 RCT or quasi-randomised trials and showed that the adverse event rate (13%) was similar to placebo (15%)[8]. However, the quality of evidence was low and not reliable[8].

A systematic review evaluating the use of IAGCI in hip OA also concluded that the procedure was well tolerated, with a rate of adverse events similar to placebo[27]. One serious adverse event, a deep venous thrombosis three months post-injection, was reported, but no clear causation was determined[28].

An RCT aiming to compare intra-articular sodium hyaluronate with methylprednisolone acetate for knee OA evaluated adverse events by recording signs and symptoms referred by the patients and by performing standard blood tests and urinalysis at baseline and at the end of the study. Although the authors only described vasovagal reactions as adverse events in this study, there is no description of what specific laboratory evaluations were made nor what changes were expected to be found[29].

While a rate of adverse events being similar to placebo seems to attest to the safety of IAGCI, we highlight that, in the case of intraarticular treatments, the rate of adverse events in the placebo groups is very relevant because it usually includes an articular puncture, with some adverse events attributed to IAGCI being probably associated with the puncture itself and all risks associated with it not the specific product used. These include some of the most common adverse events, such as injection site pain, vasovagal reactions, and, very rarely, septic arthritis. Therefore, we consider that descriptive rates of adverse events of IAGCI better inform the physician and the patient about the risks of performing an IAGCI.

A systematic literature review and meta-analysis regarding IAGCI for adhesive capsulitis reported an overall low adverse event rate of 3.9%[30]. However, only three out of the eight included RCTs mentioned safety data[30].

Overall, adverse events of IAGCI are not evaluated homogeneously across trials. Most studies do not systematically evaluate safety outcomes, and rarely are predictors of adverse events reported8,22,30. Additionally, there is significant variability in the IAGC or dosages used across studies (Table I).

Short-term local adverse events

Several short-term local adverse events, usually non-serious, have been described and should be considered (Table II). These include injection site pain, skin hypopigmentation and atrophy, and post-injection flare[30,31].

A systematic literature review and meta-analysis regarding the effect of IAGCI in knee OA evaluated 23 studies, of which 18 reported safety data[32]. The most frequently reported adverse events were injection site pain and post-injection flare[33]. While injection site pain is frequently mentioned as an adverse event, few studies report its exact incidence, which seems to vary between 1,3 to 6,8 % of procedures[34–36]. Post-injection flare is a local increase in inflammation and pain that develops within hours following the injection and can last two to three days. It has been reported in 2 to 25% of IAGCI[31,37,38]. While it is usually mild, severe cases have been reported[39]. Often, a differential diagnosis with septic arthritis is needed[40].

Skin atrophy or hypopigmentation at the injection site has also been consistently described. A retrospective study published in 2022 evaluated the use of IAGCI with triamcinolone acetonide versus hexacetonide for treating JIA[41]. This study reported only mild adverse events, such as skin atrophy or hypopigmentation at the injection site, occurring in 1.4% of patients[41]. There were no differences between groups[41]. In another study investigating the use of IAGCI in JIA, skin atrophy combined with hypopigmentation at the injection site occurred in 6.9% of the patients[42]. Of these, 71.4% were transient changes, with complete resolution occurring during the study period[42]. However, 2% of the cases were persistent[42]. An observational study focusing on US-guided IAGCI with triamcinolone acetonide in RA refractory small-joint arthritis reported four cases of depigmentation at the puncture site, all with spontaneous resolution at six months[4]. This adverse event is more frequent in older patients[40].

Tendon rupture is more relevant when considering soft tissue injections, but it has also been described as occurring in IAGCI in <1% of procedures[31].

Another rare adverse event is *embolia cutis medicamentosa*, also known as livedoid dermatitis or Nicolau syndrome. Micro-emboli obstruct a dermal artery, causing a livedoid lesion and necrotic ulcers that can be complicated by necrosis of skin, fat and muscle[40]. Nicolau syndrome's true prevalence is not known.

Short-term systemic adverse events

Vasovagal reactions have been reported with conflicting incidences, ranging from 0.7 to 20% of IAGCI[30,31]. An RCT aiming to compare the intra-articular treatment of knee OA with sodium hyaluronate versus methyl-

Table I. Variability of IAGC compounds and doses used in IAGCI

Study	IAGC used	Dose
Askari et al (2016)	Not specified	40mg
Bahadir et al (2009)	TA	20mg
Spolidoro et al, 2015	TH	6mg (PIP) 4mg (DIP)
Wang et al (2019)	TA	40mg (wrist) 20mg (MCP and PIP)
Raynauld et al (2003)	TA	40 mg
Maricar et al (2017)	MA	80 mg
Arden et al (2008)	TA	40 mg
Sadreddini et al (2009)	TA	40mg
Harhay et al (2021)	TH TA	1 mg/kg (large joints) 0.5 mg/kg (smaller joints) 1.2–1.7 mg/kg (large joints)
Robert et al (2007)	TH	40mg
Frizziero et al (2002)	MA	40mg
Lomonte et al (2015)	TH MA	40 mg 40 mg
Young omlar 2016	TA	40 mg
Rubin et al (2022)	TH TA	0,3 - 1 mg/kg (max 40mg) 0,3-1 mg/kg (max 80mg)
Marti et al (2008)	TA TH	5-40 mg according to joint size 50-75% of TA doses according to body weight
McAllindon et al (2017)	Triamcinolone	40mg
Wang et al (2022)	TA	40mg
Habib et al (2008)	TA	50mg
Russel et al (2018	TA-ER TA	32 mg 40 mg
Papavasiliou, et al 2006	MA	Dose not specified
Petersen et al (2019)	Dosing and compound bot specified	-
Park et al 2015	Triamcinolone	10 mg
Naredo et al (2002)	Triamcinolone	20mg
Sibbitt et al (2011)	TA	80 mg

IAGC - Intra-articular glucocorticoid; IAGCI - Intra-articular glucocorticoid injection; MCP - Metacarpophalangeal; PIP - proximal interphalangeal; MA – Methylprednisolone acetate; TA – triamcinolone acetonide; TA -ER - triamcinolone acetonide extended-release; TH – triamcinolone hexacetonide.

prednisolone acetate included 99 patients and reported two cases of vasovagal reactions, both occurring in the methylprednisolone group[29].

Flushing, a non-serious adverse event, occurs in 1-40% of patients up to 36 hours after the IACGI[31,34,37,43]. Some reports recognise its occurrence in about 40% of procedures. A study investigating factors influencing the efficacy of IAGCI in patients with JIA described flushing in 1.1% of patients and increased appetite and mood changes in 3.4% of patients[42].

Headaches were also described after IAGCI[24], with a study reporting an incidence of 18% in knee OA patients treated with triamcinolone acetonide[44].

Transient hyperglycaemia can occur after IAGCI in diabetic patients[45]. Therefore, EULAR suggests blood glucose monitoring after IAGCI, particularly from the first to the third day[46], as blood glucose levels seem to increase during days 1–3 post-injection[45]. This concern seems to be more relevant in patients with suboptimal diabetes control. A prospective study evaluating hyperglycaemia after triamcinolone injections included 70 patients, most of whom received only one injection, while nine received two, and two received three simultaneous injections. Most procedures consisted of IAG-

Table II. Short-term local and systemic adverse events of IAGCI – reported incidences

Adverse events	%
Local adverse events	
Post-injection flare	2-25%
Skin atrophy and hypopigmentation	1.4 – 6.9%
Injection site pain	1,5-6,8%
Tendon rupture	<1%
Nicolau syndrome	-
Systemic adverse events	
Vasovagal reaction	0.7-20%
Flushing post-procedure	1-40%
Headache	18%
Septic arthritis	0,0003% to 0.0357%
Clinically relevant bleeding	0-0.2% (patients under antithrombotic drugs)
Iatrogenic adrenal suppression	-
Tachon syndrome	-
Anaphylactic shock	-

- : incidence not reported. IAGCI - Intra-articular glucocorticoid injection;

CI, but ten peri-articular injections were included (9 trigger fingers and 2 wrist tendon sheaths). This study showed that preinjection haemoglobin A1C significantly influences post-injection blood glucose[47]. On the other hand, the patient's body mass index, insulin use, glucocorticoid dosage, and the number of injections performed had no significant effect on the elevation of blood glucose[47]. For diabetic patients, extended-release triamcinolone acetonide could be an alternative since it may increase glycaemia less than immediate-release triamcinolone acetonide[48]. Despite frequently rising blood glucose levels, no severe adverse events such as hyperosmolar hyperglycaemic state or ketoacidosis have previously been reported after IAGCI[45,47].

Other systemic adverse events are exceedingly rare and include secondary adrenal insufficiency and injection-related Tachon syndrome[8,14,49]. Iatrogenic adrenal suppression may occur following a single intraarticular or soft tissue glucocorticoid injection and may last up to two weeks, putting patients at risk for an adrenal crisis in case of trauma, infection, or surgery[50,51]. Anaphylactic shock has been described before but is extremely rare[52]. Finally, we found a single report describing a case of acute glucocorticoid-induced myopathy, after a fluoroscopy-guided triamcinolone/ropivacaine mixture injection for shoulder OA, in a young and otherwise healthy and active male[53].

The septic threat

Infectious complications such as septic arthritis are the most worrisome short-term adverse event of IAGCI. Septic arthritis is a serious adverse event that can lead to severe sepsis and death. It is associated with significant morbidity (31.6%), including osteomyelitis and deterioration of joint functional outcomes, and a high mortality rate (11.5%)[37].

Reported frequencies vary from 0.0003% to 0.001%[37,46,49,54]. A study on septic arthritis reported a possible increasing incidence (0.0357%), which the authors suggest might be related to the higher number of intra-articular procedures[55], but care should be taken with the interpretation of these data, considering the retrospective nature of the study. Another issue raised by the authors, but not undoubtedly supported by evidence, is the relationship between the increasing incidence of septic arthritis and the increasing number of intra-articular procedures performed by general practitioners[55], which could suggest that procedures performed by doctors specialised in musculoskeletal diseases could incur in fewer adverse events. A retrospective study also suggests that the experience of the rheumatologist, as well as the use of prefilled sterile syringes, could correlate negatively with the development of septic arthritis56.

It has been extensively demonstrated that patients with rheumatic diseases, including RA and other inflammatory arthropathies, have an increased risk of infection, including septic arthritis, compared to the general population[37]. This is probably due to a state of immunodeficiency and joint damage associated with the disease[37]. Despite this, there is limited evidence on whether there is a relationship between the development of septic arthritis after an IAGCI and a patient's diagnosis or therapy (i.e. immunosuppression). However, a higher incidence of septic arthritis (including cases after IAGCI) in RA patients on immunosuppressive therapy has been reported previously[55,57].

Bleeding risk – a continued conundrum

Bleeding risk is also a relevant concern when considering IAGCI. It has been repeatedly shown that IAGCI is not contraindicated in people with clotting/bleeding disorders or taking antithrombotic medications (antiplatelet agents, low-molecular-weight heparin, warfarin or direct oral anticoagulants) unless the bleeding risk is high at the time of the procedure. In patients with a clotting-impairing haematological disease, US-guided injections were safe when performed after appropriate factor replacement[58]. Bleeding risk in patients on antithrombotic drugs was between 0% and 0.2%[59,60]. There seems to be no significant difference in early or late adverse events in patients receiving therapeutic warfarin (INR ≥2)[59]. A retrospective study of 640 arthrocentesis and intra-articular injections performed in 514 antico-

agulated patients reported only one procedure (0.2%) that resulted in early and clinically significant bleeding[59]. This occurred in the fully anticoagulated group (INR ≥2), with no statistical differences compared to patients with lower INR[59]. Continued therapy with the novel oral anticoagulants (NOACs) also seems safe60 for arthrocentesis and intra-articular injections - a retrospective study reported no bleeding complications in 1050 procedures[60]. However, most data are based on retrospective, non-randomised data, including only patients receiving anticoagulants and no proper control groups. More recently, a systematic literature review, which included seven studies with patients on warfarin, acenocoumarin, and direct oral anticoagulants, also concluded that joint injection seems safe in patients on anticoagulants[61]. The authors also highlighted that bleeding risk was not different according to the injected joint, chosen approach (US-guided or conventional), withholding or reversal (with vitamina K, for example) of anticoagulation, bridging with low molecular weight heparin, renal or hepatic impairment or concomitant antiplatelets[61].

Long-term adverse events – the cartilage question

Considering possible long-term adverse events, case reports and some retrospective studies have previously suggested a link between IAGCI and the development of destructive OA of the hip in patients with a previous diagnosis of hip OA[62–64]. A retrospective single-centre study with a small sample of patients reported an incidence of 21%[62]. In this study, which included 109 patients, IAGCI was performed under fluoroscopic guidance with 1 ml of triamcinolone (40 mg/ml). Radiographs were performed within six months before and one year after the injection, and the diagnosis of rapidly destructive hip OA was established by radiographic evidence of progressive loss of cartilage (greater than 2 mm or 50% joint space narrowing) over 12 months or less, irrespective of reported symptoms[62]. The same study suggests that older age and being Caucasian may increase the risk for a negative joint outcome after IAGCI[62]. Another retrospective study including 70 patients submitted to hip IAGCI (40 mg triamcinolone plus 4 ml of ropivacaine 0.5%) showed a higher rate of osteoarthritis progression (44% vs 24%) and development of femoral head collapse (17% vs 1%) when compared with patients with hip pain who did not receive an injection[64].

While less catastrophic than rapidly progressive OA, some concerns have been raised regarding the potential long-term adverse events of IAGCI on hyaline cartilage (mainly cartilage loss)[65]. A cohort derived from the osteoarthritis initiative (a multi-centre longitudinal observational study of risk factors for both incident and progressive knee OA), including 148 patients submitted to IAGCI and 536 controls, concluded that IAGCIs, especially repeated IAGCI, appeared to be associated with an increased risk of knee radiographic OA progression[65]. A previous RCT reported results that contrast with this observational study, showing no loss of joint space in a two-year follow-up (defined through conventional radiography criteria) when comparing saline injections and IAGCI with 40 mg triamcinolone acetonide, although the sample was small, with only 34 patients included in each group[7]. Another RCT showed a statistically significant difference in cartilage loss (determined by Magnetic Resonance Imaging) at two years, also when comparing triamcinolone acetonide with saline, but the true clinical significance of these changes is unknown regarding pain and function[34]. Of note, in both these RCTs, IAGCIs were performed every 12 weeks for 2 years, which may suggest that detrimental cartilage effects may be a concern with repeated injections[7,34]. A 2015 RCT of IAGCI with 40 mg triamcinolone acetonide vs saline in patients with symptomatic OA (with IAGCI performed every three months for two years) showed a greater rate of loss of cartilage thickness (however small in magnitude), detected by MRI in the treated group[66]. We found no RCTs aiming to compare different IAGC compounds for this endpoint.

Despite some concerns based on low-quality data, the actual risk of significant acceleration of OA progression seems to be low or inexistent[37], and the benefits probably outweigh the potential harm of IAGCI on hyaline cartilage[7]. Still, most of the available data is related only to the knee joint[7,66]. Overall, while there seems to be evidence that IACGI may accelerate cartilage loss, no direct correlations with clinical patient outcomes have been demonstrated thus far.

Are there differences between imaging-guided vs non-guided procedures?

The 2021 European Alliance of Associations for Rheumatology (EULAR) recommendations for intraarticular therapies suggest that imaging guidance (usually using US) may be used to improve accuracy[46]. Although US-guided intraarticular therapies improve the procedure's accuracy[67–69], systematic literature reviews (including RCTs and non-RCTs) showed that clinical outcomes, such as pain and function, are similar in the long-term (> 6 weeks)[70].

Few comparisons between the rate of adverse events in unguided versus US-guided intraarticular procedures have been published. A study designed to evaluate the unguided sacroiliac IAGCI effect on refractory buttock pain in spondylarthritis patients reported no joint infections or other local or systemic adverse events re-

lated to unguided injections, but no comparison was made to US-guided procedures[17].

An RCT of US-guided IAGCI in inflammatory arthritis (that included small-, intermediate- and large-joint injections, mainly in RA patients) reported a significant reduction in procedural pain compared to unguided IAGCI[71]. The authors theorised that better control and direction of the needle tip away from pain-sensitive structures could explain these differences[71]. Additionally, the cooling effect of US gel, the pressure from the US transducer, and the distracting effect of observing the sonographic image were also suggested as positive contributors[71]. Regarding injection site pain, sonographic needle guidance has been shown to reduce procedural pain, both at needle introduction and post-injection pain[70–72]. However, we found no reports of differences regarding any other adverse event. A retrospective study regarding palpation- versus US-guided acromioclavicular joint IAGCI highlighted two cases of skin atrophy and depigmentation in the palpation-guided group, although this did not represent a statistically significant difference[12].

Regarding the use of fluoroscopy, data is more limited. A prospective RCT that included 120 patients aimed to compare the short-term efficacy and safety of US-guided versus fluoroscopy-guided sacroiliac joint (SIJ) injections in patients with noninflammatory SIJ dysfunction. This study reported pain in the periosteum caused by needle irritation during the injection in four patients in the fluoroscopy-guided group and one in the US-guided group. Additionally, leg weakness caused by sciatic nerve block was reported in two and three patients in the fluoroscopy and US-guided groups, respectively. These differences were not statistically significant[73].

More commonly, no adverse events are reported in studies comparing fluoroscopic guidance with US or anatomical reference[74,75], but overall data quality from these studies is low.

Radiation exposure and its associated risks also have to be taken into account when considering fluoroscopy[73].

Predictors for specific adverse events – a future role in risk profiling?

When recommending a specific treatment for a particular patient, clinicians should consider, besides the indication for treatment, other patient-related variables such as the capacity to comply, comorbidities and concomitant medications that may influence treatment efficacy and safety. This principle should apply to local treatments as well. However, there is a severe unmet need in the IAGCI literature regarding safety data, especially predictors of adverse events.

A retrospective study evaluated the risk of septic arthritis in patients who received an IAGCI (0.08%)[76]. Male gender, advanced age, and pre-existing joint disease were identified as risk factors[76]. There were no differences in risk of infection related to specific pre-existing diagnoses, and there was no information related to concomitant therapy[76].

Another retrospective study reported the infectious related outcomes of 144 patients who had undergone total knee replacements. Of these, 54 had been previously submitted to an IAGCI. Six patients developed deep tissue infections, five of whom had previously been submitted to IAGCI. The authors raised the concern that pre- and peri-operative IAGCI could be associated with a higher incidence of postoperative infectious complications77. Nonetheless, it is worth mentioning that the IAGCI were performed 8-25 months before the surgical procedure.

We found no prospective, randomised or non-randomised clinical trials that systematically evaluated any other predictors of IAGCI adverse events.

Identifying such hypothetic predictors could also help guide the clinician in choosing the best treatment course for the individual patient and better inform patients about available options.

CONCLUSIONS

While several local and systemic adverse events have been identified and described, the available literature is overall of low quality, and the incidence of these adverse events varies greatly between reports. One of the reasons for this is that few studies described these adverse events as the primary focus.

Overall, the most common adverse events are post-procedure flushing (1-40%) and vaso-vagal reactions (0.7-20%). Post-injection flare is the most common local adverse event (2-25%). Infection is rare but is a major concern due to the high morbimortality. Recent data regarding bleeding risk is reassuring, attesting to the safety of maintaining anticoagulant therapy. This is particularly relevant considering that increased thrombotic risk is not null even with a short interruption of anticoagulation78,79. Ultimately, individual risk stratifying should prevail in these cases.

Another pressing issue regarding IAGCI is the limited data available on comparing different compounds. Triamcinolone acetonide is the most frequently used glucocorticoid in IAGCI efficacy and safety studies. While efficacy data seems to favour triamcinolone acetonide[21], comparative safety evaluations are clearly lacking. A retrospective study published in 2022 evaluated the use of IAGCI with triamcinolone acetonide versus hexacetonide for treating JIA[41] and found no difference

between groups regarding side effects[41]; for diabetic patients, extended-release triamcinolone acetonide seems to increase glycaemia less than immediate-release triamcinolone acetonide[48], but no comparison with other compounds was carried out.

The low quality of data impairs the clinician's capacity to inform patients correctly about these invasive procedures. Since IACGI is a routinely used treatment option, more detailed knowledge of adverse events is warranted. Knowledge gaps regarding the safety of IACGI include the rate of specific adverse events, whether there are differences regarding the safety of different glucocorticoids, the use of US to guide the procedures, the indication for the procedure (inflammatory versus OA), comorbidities (such as fibromyalgia or anxiety), and concurrent systemic therapies (such as immunosuppressants). Knowing specific adverse event predictors would also help clinicians to choose the best treatment option for the individual patient.

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