Consensus

Application of Glucocorticoids in Minimally Invasive Interventional Pain Management: Chinese Expert Panel-Based Guideline: Expert Panel of Special Training Project on Pain Management of National Health Commission Capacity Building and Continuing Education Center

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Background: Glucocorticoids (GCs) are widely used in clinical practice. Through minimally invasive intervention technology, GCs act on lesions accurately. This route of administration is superior to others. However, GCs are often applied irrationally, and serious adverse reactions frequently ensue.

Objectives: The aim of this review is to provide an expert consensus for the application of GCs in minimally invasive interventional-administration routes and thereby develop a consistent philosophy among the many diverse groups interested in the use of GCs.

Setting: The Expert Panel of Special Training Project on Pain Management of National Health Commission Capacity Building and Continuing Education Center.

Methods: We set up the Expert Panel of Special Training Project on Pain Management of National Health Commission Capacity Building and Continuing Education Center from various specialties and groups and performed the study of GC-related objectives and vital issues. The center reviewed the literature on the use, effectiveness, and adverse outcomes of GCs in accordance with evidence-based medicine principles, evaluated the quality of evidence by synthesizing existing literature, and utilized grading for recommendation.

Results: The grading recommendations for the application of GCs were formed to standardize said application. The center recommended that the principles of minimally invasive intervention of GCs be as follows: 1) Suspending GCs is not recommended for the cervical and thoracic epidural block or the radicular block if imaging monitoring is unavailable; 2) For drug compatibility, drugs other than normal saline, local anesthetics, and GCs are not recommended; 3) For treatment of epidural and selective radicular blocks within 6 months, intermediate- and long-acting GCs should not be used more than 3 times, while short-acting GCs should not be used more than 5 times; 4) GCs can be injected intraarticularly once every 3 months for up to 2 consecutive years. The frequency of intraarticular GC injections should be determined based on the severity of the patient's conditions and symptoms, as well as the preferences of the medical staff and patient; 5) GCs are not recommended for sympathetic blocks. In addition, the expert team made detailed grading recommendations for the indications, contraindications, minimally invasive interventional-administration routes, and specific operations of GCs.

Limitations: Lack of high-quality RCTs.

Conclusions: The expert consensus was established on the basis of comprehensive review of the literature and consensus among the panelists. Consequently, different minimally invasive routes of GC administration recommend different doses and courses to standard the use of GCs.

Key words: Expert consensus, glucocorticoids, minimally invasive intervention, application

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Glucocorticoids (GCs) are widely used in clinical practice due to their anti-inflammatory, antitoxic, anti-shock, and immunosuppressive effects. In recent years, minimally invasive interventional therapy has developed rapidly in the pain clinics with a high prevalence rate because of its increasingly mature technique, through which low doses of GCs are delivered precisely on the lesions to relieve or eliminate pain as local inflammatory responses are rapidly lowered with fewer systemic adverse reactions and good therapeutic effects. This method is superior to other approaches of administration (1). With the continuous development of various minimally invasive interventional methods and guiding techniques, as well as the development of new dosage forms of GCs, doctors in various departments have more choices in clinical treatment. However, GCs have been also used unreasonably from time to time, even in ways that have led to serious adverse reactions. Therefore, how to standardize the administration of GCs, maximize the advantages of their local application, and avoid or reduce adverse reactions in minimally invasive interventional pain management has become an important topic that doctors of all disciplines have to face.

GCs are widely injected through the periarticular, peri-musculotendinous, and peri-ligamentous areas, via the myofascial trigger point (MTrP), intraarticularly, around the nerves (nerve ganglions, plexuses, stems, and terminals), and epidurally, all of which are effective routes of administration for chronic pain treatment. Nonetheless, there are still controversies over the indications, specific application, and usage of GCs. Therefore, we established an expert panel to study the common issues in the daily management of GCs and developed recommendations correspondingly, using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach (2). Our process is broken down thusly:

Methods

We began with the identification of clinical issues, followed it with a systematic literature search and evidence summary, and ended with expert recommendations made through feedback.

Multidisciplinary Expert Panel

The panel consisted of 10 pain physicians and 5 orthopedic surgeons.

Organizers and Coordinators

Yanqing Liu and Ke Ma.

Panelists

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Scope Determination

These recommendations were involved in indications for GCs, their routes of administration, and their usage. Said recommendations were adopted by physicians (mainly pain physicians) and other medical personnel concerned with their patients' pain. Core leaders among those physicians raised the following clinical questions upon project supervision and coordination: What are the indications of GCs? What are the routes of administration of GCs? How shall we use GCs? What shall we pay attention to during their use?

Literature Search

Literature reviewers were assigned to different topics according to their specialties, with 3-4 experts focusing on 2-3 clinical topics. The literature was limited to articles in English or Chinese, including systematic reviews, randomized and non-randomized controlled trials, observational cohorts, and case series published in peer-reviewed journals via PubMed/MEDLINE, Embase, Cochrane, China Journal Net, and Wanfang Database. In accordance with the GRADE approach, the quality of the available evidence (graded as high, medium, low, or very low) was determined by the risks of bias, inaccuracy, and inconsistency (Table 1). At least one recommendation was developed for each topic.

Recommendation Development

An expert panel assessed the feedback on the recommendations and evidence provided by the literature reviewers, rated the necessity of each project, and selected recommendations in the first round of the meeting. Recommendations were eliminated, restructured, or consolidated because of poor quality or conflicting evidence. As specified by the GRADE approach, the voting expert panel developed recommendations (strong recommendation, weak recommendation, or no consensus) based on the compromise among favorable and unfavorable effects and quality of evidence in the second round of the meeting (Table 1).

To standardize the reasonable application of GCs in minimally invasive interventional pain management, improve their therapeutic effects, ensure the safety of patients during medication, and comply with the

principles of health economics, the Expert Panel of Special Training Project on Pain Management of National Health Commission Capacity Building and Continuing Education Center further incorporated more research results following evidence-based medicine based on the relevant previous expert consensus. After soliciting extensive opinions from all parties, our expert panel composed the present document.

Pharmacological Effects of GCs on Pain

GCs play an important role in maintaining normal physiological homeostasis in the body and an adaptive and protective role during internal and/or external stress by acting on almost all body tissues. These roles include exerting an anti-inflammatory effect, changing the metabolism of carbohydrates, proteins, and lipids, maintaining the fluid and electrolyte balance, and protecting the nervous system and the cardiovascular, renal, skeletal muscle, immune, and endocrine functions (3).

Among these properties, the powerful anti-inflammatory effect constitutes the pharmacological basis for the use of GCs in pain management. During the early stage of inflammation, GCs can reduce the permeability of capillaries, exudation, and release of inflammatory factors in addition to inhibiting the aggregation of inflammatory cells. By these actions, GCs improve symptoms caused by aseptic inflammation, such as redness, swelling, heat, and pain. In the late stage of inflammation, GCs can inhibit the proliferation of capillaries and fibrous tissues as well as collagen synthesis, delay the formation of granulation tissues, prevent adhesion and scar formation, and hence reduce the occurrence of sequelae.

The anti-inflammatory effect of GCs is exerted by regulating gene expression, specifically binding to GC receptors in either the cell membrane or cytoplasm, nonspecifically changing the physicochemical properties of the cell membrane, and affecting ion permeability or activating membrane receptor proteins. GCs regulate gene expression by promoting or inhibiting the transcription of target genes, thus inhibiting the transcription of pro-inflammatory molecules while inhibiting the expression of inflammatory genes by interacting with other transcription factors (4). The gene-regulation effect of GCs is characterized by slow onset and lasting effect.

GCs achieve not only analgesia mainly through the direct effect of anti-inflammation and cell membrane stabilization and the possible effect of unmyelinated C-fiber neurolysis (5) but also chronic pain management. The latter effect is achieved by reducing capillary endothelial permeability to maintain microcirculation at inflammation sites, prevent edema formation, and regulate the immune response. In addition, GCs can inhibit phospholipase, which is necessary for the inflammatory chain reaction along the cyclooxygenase and lipoxygenase pathways.

Table 1. *Qualitative modified approach to grading of evidence.*

Quality of Evidence	Definitions
High (A)	Further research is very unlikely to change our confidence in the estimate of the effect.
Moderate (B)	Further research is likely to have an important impact on our confidence in the estimate of the effect and may change the estimate.
Low (C)	Further research is very likely to have an important impact on our confidence in the estimate of the effect and is likely to change the estimate.
Very low (D)	Any estimate of the effect is very uncertain.

The main mechanism of GCs' local analgesic action is the inhibition of peripheral and central sensitization in chronic pain (6). GCs can inhibit peripheral sensitization by inhibiting prostaglandin synthesis and inflammatory cytokines, reducing inflammatory edema of damaged nerve roots, improving microcirculation, avoiding ischemic nerve injury, and inhibiting the ectastic discharge in dorsal root ganglion neurons and the coupling of dorsal root ganglion neurons with sympathetic postganglionic fibers. Furthermore, GCs can also reduce central sensitization by inhibiting the excitability of spinal dorsal horn neurons and the activation of gliocytes.

Independently of their receptors, GCs can produce nonspecific effects within seconds or minutes. Studies on the nongenomic effects of GCs are expected to enhance the hormones' anti-inflammatory effects and reduce the side effects (7,8). In addition, GCs can also prolong the action time of local anesthetics by constricting blood vessels, reducing the permeability of capillaries, and lowering the vascular absorption of local anesthetics.

Classification and Dosage Forms of GCs

GCs can be categorized by duration of action as short-acting, intermediate-acting, or long-acting. Alternatively, GCs can be classified by the intensity of anti-inflammatory action as weak, moderate, or po-

tent. In terms of anti-inflammatory potency, prednisolone, methylprednisolone, triamcinolone acetonide, dexamethasone and betamethasone are, respectively, 4, 4, 5, 30 and 25~30 times as potent as hydrocortisone, at a potency of one (as a reference). Synthetic GCs can also be classified into the granular and nongranular categories according to water solubility and polymerization properties. Steroids are often prepared into either lyophilized powder or suspension because their particulates are not easy to dissolve in water, resulting in aqueous solutions that can easily precipitate out. Clinically common GCs may vary in their effect characteristics after being prepared into different dosage forms (9). Some pharmacological properties, relative potencies, and equivalent doses of GC injections commonly used in minimally invasive interventional pain management are shown in Table 2.

Commonly used GC injections in minimally invasive interventional therapy for pain mainly include the following dosage forms:

(1) Water-soluble Formulations

Common formulations are represented mainly by dexamethasone phosphate, betamethasone phosphate, and methylprednisolone acetate, which act quickly, are absorbed easily, and pose little irritation to tissues. However, these formulations have short local anti-inflammatory effects.

(2) Suspension Formulations

Common formulations include mainly triamcinolone acetonide and compound betamethasone (Diprosone), which are not allowed for intravenous injection. Triamcinolone acetonide, slowly dissolved and released in the tissues, can act for a long time (2~3 weeks), but it causes great local irritation. This formulation is not suitable for multiple injections because long-term large doses will lead to crystallization and precipitation and therefore tissue adhesion. Diprosone is a fast-acting, long-acting, and potent GC compound composed of 2 mg betamethasone sodium phosphate and 5 mg betamethasone dipropionate. After local injection, betamethasone sodium phosphate is dissolved easily in water and quickly absorbed for action. The compound then reaches peak plasma concentration one hour later. Meanwhile, betamethasone dipropionate, which is slightly soluble in water, is absorbed slowly and then acts for more than 4 weeks. Because betamethasone dipropionate is the suspension of hemispherical crystallites, it can be used repeatedly compared to triamcinolone acetonide and other preparations, since betamethasone dipropionate causes little local irritation.

(3) Emulsion Formulations

Dexamethasone palmitate (Limethason) is commonly used as a preparation of lipid microspheres with long action and sustained release, characterized by good targeting, efficacy, and safety, which can prevent the crystallization of precipitates in suspension and capillary blockage. This formulation can be safely injected intraarticularly or intravenously for a radicular or cervical and thoracic epidural block.

(4) Powder-injection Formulations

At present, GC powder-injection formulations are represented mainly by methylprednisolone sodium succinate (Medrol) and triamcinolone acetonide. The post-dissolution usage and therapeutic characteristics of these formulations are the same as those of their water-soluble counterparts.

Table 2. *Characteristics of glucocorticoids*.

Drug Name	Receptor Affinity	(ratio)	Duration of Action	Anti-Inflammatory Potency	Effect of the Water-SaltMetabolism	Effect of Glucose metabolism	Suppression Time of the HPA Axis	Equivalent Dose
			(hours)	(ratio)	(ratio)	(ratio)	(days)	(mg)
Short-acting	Hydrocortisone	1	8~12	1	1	1	1.25-1.5	20
	Prednisolone	0.8	12~36	4	2.2	4	1.25-1.5	5
	Methylprednisolone	0.25~0.5	12~36	5	11.9	5	1.25-1.5	4
	Triamcinolone acetonide	±	36~54	5	1.9	5	1.25-1.5	4
Long-acting	Dexamethasone	±	36~54	30	7.1	20~30	2.75	0.75
	Betamethasone	±	36~54	25~30	5.4	20~30	3.25	0.6

Note: In the table, the ratios of water-sodium retention and of anti-inflammatory potency are calculated by taking hydrocortisone as the baseline (value of one) while the equivalent dose is calculated by taking hydrocortisone as the standard, and ± represents being almost zero.

Indications and Contraindications

Indications

1. Aseptic inflammation of soft tissues (10): myofasciitis (11-13), tendonitis (14,15), bursitis/synovitis, popliteal cyst (16), tenosynovitis (17), external humeral epicondylitis (18), scar pain (19), rotator cuff disease (20,21), frozen shoulder (22-24), acromial impingement syndrome (25), piriformis syndrome (26), etc.
2. Pain associated with bone and joint diseases: knee arthritis (27-30), hip arthritis (31,32), finger arthritis (33,34), sacroiliac arthritis (35), temporomandibular arthritis (36), etc.
3. Spine-related pain: protrusion of intervertebral disc (37-39), spinal canal stenosis (40,41), etc.
4. Neuropathic pain and complex regional pain syndrome (42,43): postherpetic neuralgia (44), trigeminal neuralgia, stump pain, neuroma (45), ganglion cyst (46), chronic groin pain (47), etc.
5. Pain associated with autoimmune rheumatic diseases: rheumatoid arthritis (48), ankylosing spondylitis, etc.
6. Cancerous pain (49,50).
7. Pain associated with metabolic diseases: gout (51), osteoporotic compression fracture (52), etc.

Contraindications

1. Absolute contraindications: (1) allergy to GCs or solvents, (2) severe skin rupture or fracture, (3) infection at injection sites, (4) bacteremia and sepsis, (5) uncontrollable coagulopathy.
2. Relative contraindications: (1) severe mental illness, (2) peptic ulceration in unsteady stage, (3) first trimester, (4) severe hypertension and poor glycemic control, (5) hypercortisolism, (6) other conditions unsuitable for medication.

GC Application: Routes of Administration and Operation of Minimally Invasive Intervention

Principles

1. The suspension of GCs is not recommended for radicular or cervical and thoracic epidural blocks if imaging monitoring is unavailable (53).
2. For the sake of drug compatibility, drugs other than normal saline, local anesthetics, and GCs are not recommended.
3. When patients are being treated with epidural or selective radicular blocks, intermediate- and long-acting GCs should not be used more than 3 times within 6 months while short-acting GCs should not be used more than 5 times within the same time frame.
4. GCs can be injected intraarticularly once every 3 months for up to 2 consecutive years. The frequency of intraarticular GC injections should be determined based on the severity of the patient's conditions and symptoms, as well as the preferences of the medical staff and patient.
5. GCs are not recommended for sympathetic blocks.

Table 3. *Guide for strength of recommendations.*

Intensity of Recommendations	Definitions
Strong recommendations (1)	Consistent recommendation (agreement in ≥ 80% of the participants)
Weak recommendations (2)	Basically consistent recommendation and little controversy (agreement in 60%-80% of the participants)
No consensus (3)	No consensus and great controversy (agreement in < 60% of the participants)

Specification for Operation and Precautions

When referring to the Chinese Specification for Pain Management, the following items should be noted: (1) The dosage form, dose, drug compatibility, and treatment course of GCs with different administration routes should be selected reasonably. (2) Strict aseptic operation, enhanced monitoring of vital signs, and prevention of adverse reactions should be performed. (3) Precise positioning should be performed. It is recommended that precise positioning be performed under the guidance of x-rays/nerve stimulator/ultrasonography. If necessary, angiography can be performed to confirm the puncture site. (4) It is recommended that trained specialists perform the operation.

Peri-articular, peri-musculotendinous, and peri-ligamentous injection, myofascial trigger point (MTrP) injection, intraarticular injection, injection around nerves (nerve ganglions, plexuses, stems and terminals), epidural injection, and more are effective routes of administration for chronic pain treatment. Details are as follows:

1. Peri-articular, peri-musculotendinous, peri-ligamentous and MTrP injection

In general, drugs (local anesthetics with GCs) are injected directly and accurately at pain sites around the diseased joints, tendons, and ligaments or MTrPs (54) to achieve local anti-inflammatory and analgesic

effects. Ultrasonic guided injection is more accurate and more effective than traditional unguided puncture (55).

1.1 Intradermal (subcutaneous) injection is not recommended for exposed parts, such as the head and face.
Compatibility: 0.5% lidocaine or 0.15% ropivacaine + 1 mL Diprosone or 3~5 mg dexamethasone or 1 L dexamethasone palmitate.
Volume: 0.5~1 L for each site, a total of 10~40 mL.
Course of treatment: once every 2~4 weeks, 3~5 times per year.

1.2 Injection at the origins and terminations of muscles and bursa
Compatibility: 0.5% lidocaine or 0.15% ropivacaine + 1~2 mg dexamethasone or 0.2~1 mL Diprosone or 1 mL dexamethasone palmitate (56).
Volume: 1~5 mL.
Course of treatment: once every 2~4 weeks, 2~4 times per year.

1.3 MTrP injection
Compatibility: 0.5% lidocaine or 0.15% ropivacaine.
Volume: 0.5~2 mL.
Course of treatment: undetermined.
Hormones are not recommended.

2. Intraarticular injection
Because different joints in the whole body have corresponding puncture approaches, an injection volume should be selected reasonably according to the volume of the joint cavity. It is recommended to perform intraarticular injection under imaging orientation to ensure that the drug enters the joint cavity. The knee-cavity injection can often be performed from the upper lateral patella precisely without guidance (57,58). There is no clear conclusion on the interval between intraarticular GC injections, and some reviews have recommended that the interval between 2 injections should not be less than 3 months (59). The guidelines for the diagnosis and treatment of osteoarthritis (OA) in China (2019 edition) recommended that the interval of intraarticular GCs injections be no shorter than 4-6 months for patients with persistent pain or moderate to severe pain associated with knee OA (60). The frequency of intraarticular GC injections should be determined based upon the severity of the patient's conditions and symptoms, as well as the preferences of the medical staff and patient.

2.1 Peri-articular injection
Compatibility: 1% lidocaine or 0.15% ropivacaine + 0.5~1 mL Diprosone or 10~40 mg triamcinolone acetonide or 1 mL dexamethasone palmitate. (Dose increment or decrement based on individual differences and different joints. See below.)
Volume: 0.5~1 mL
Course of treatment: no more than once in 3 months, with an interval of 3~4 months.

3. Injection around nerves (nerve ganglions, plexuses, stems, and terminals)
It is recommended that precise positioning be performed under the guidance of x-rays/nerve stimulator/ultrasonography. If necessary, angiography can be performed to confirm the puncture site and thereby achieve a better effect. The closer the puncture needle is to the nerve, the better the consequent effect. However, seeking paranesthesia is unnecessary (61).

3.1 Selective cervical/thoracic radicular blocks at the cervical/thoracic segments
Compatibility: 0.1% lidocaine or 0.15% ropivacaine + 1 mL dexamethasone palmitate.
Volume: 2~4 mL.
Course of treatment: once every 2~4 weeks, no more than 3 times per year.

3.2 Selective lumbar radicular block at lumbar segment (62)
Compatibility: 1% lidocaine or 0.2% ropivacaine + 1 mL Diprosone or 10~40 mg triamcinolone acetonide or 1 mL dexamethasone palmitate (63).
Volume: 2~10 mL
Course of treatment: once every 2~4 weeks, no more than 3 times per year.

4. Epidural injection
There are a variety of approaches for epidural puncture, such as the transforaminal, the interlaminar, and the sacral canal. Epidural injection of GCs can reduce the inflammatory response in or around nerves and play anti-inflammatory and analgesic roles (64). Better clinical effects can be achieved via the transforaminal approach, and the therapeutic effect achieved by trained specialists is significantly better than that achieved by nonspecialists (65-67).

To avoid serious complications, only nongranular GCs can be used during cervical epidural injections via the transforaminal approach. During an epidural injection, it is recommended that the contrast agent be injected under imaging guidance and real-time fluoroscopy (53).

4.1 Epidural block at the cervical/thoracic segment
Compatibility: 1% lidocaine or 0.15% ropivacaine + 1 mL dexamethasone palmitate.
Volume: 2~4 mL.
Course of treatment: once every 2~4 weeks, no more than 3 times per year.

4.2 Epidural block at the lumbar segment
Compatibility: 1% lidocaine or 0.2% ropivacaine + 1 mL Diprosone or 10~40 mg triamcinolone acetonide or 1 mL dexamethasone palmitate (63).
Volume: 2~10 mL.
Course of treatment: once every 2~4 weeks, no more than 3 times per year.

4.3 Sacral canal injection
Compatibility: 0.5% lidocaine or 0.1% ropivacaine + 1 mL Diprosone or 10~40 mg triamcinolone acetonide or 1 mL dexamethasone palmitate (1).
Volume: 10~20 mL.
Course of treatment: once every 2~4 weeks, no more than 3 times per year.

5. Subarachnoid injection
Although this route of administration for chronic pain remains controversial, all types and dosage forms of GCs other than dexamethasone are contraindicated for use in the subarachnoid cavity.

Adverse Reactions and Their Prevention and Treatment

GCs used for minimally invasive interventional pain management induce fewer local and systemic adverse reactions, with incidence, type, and degree thereof dependent on the variety, dose, dosage form, and usage of the drug. Imaging-guided puncture and repeated resorption during injection are recommended for effectively reducing the incidence of adverse reactions (68). During treatment with epidural injections (especially at the cervical segment), GC suspension is either not recommended or is used with great caution, considering the serious complications, such as spinal cord injuries, infarctions, and even strokes, reported after intrathecal or intravascular injections. When GC suspension must be used (to reiterate, especially at the cervical segment), precautions such as the use of a puncture needle with a blunt tip, the injection of contrast agents under real-time imaging monitoring, and pre-testing with small doses of local anesthetics must be taken (69). The following numbered list breaks down the protocol in more detail.

1. Local adverse reactions and complications and their prevention and treatment

1.1 Bleeding and infection at injection sites
Aseptic operations should be standardized. If symptoms of infection occur, a standard anti-infective treatment should be given in time.

1.2 Incorrect approach to blood vessels or subarachnoid cavity
GCs must be withdrawn before and during injection to avoid approaching the blood vessel or subarachnoid space. Once abnormal conditions are observed, the injection should be stopped immediately, and the abnormalities should be closely observed and treated in time.
If thrombosis occurs after the intra-arterial injection of a GC suspension, it may induce serious complications, including spinal infarction, paraplegia, and death (in rare cases).

1.3 Soft tissue calcification after tendon and ligament injury/fracture
Attention should be paid to injection resistance during peri-musculotendinous and peri-ligamentous injection while avoiding intra-tendinous injections.

1.4 Atrophy and hypopigmentation of subcutaneous tissues
Either the intradermal injection of exposed parts, such as the head, face, and limbs, or an excessive injection volume, resulting in excessive tension in the tissue, should be avoided.

1.5. Intraarticular injection: crystal-induced synovitis and destruction of articular cartilage.

1.6. Nerve injury

2. Prevention and treatment of systemic adverse reactions

In standard and reasonable minimally invasive interventional pain management, local GC injections may rarely induce systemic adverse reactions. However, long-term large-dose local application of GCs may also result in systemic symptoms. Some studies have shown that local use of GCs may lead to changes in bone metabolism, immunosuppression, and the neuropsychiatric system. According to the available evidence, the maximum systemic cumulative dose of triamcinolone acetonide/methylprednone is 200 mg per year and 400 mg per 3 years for postmenopausal women and men above 50 years old. Patients with osteoporosis, including those with fragility fractures, may be treated with bisphosphonates if they receive multiple injections. In most cases, it is recommended that epidural and intraarticular injections be given only when a patient's fasting blood glucose level is below 200-250 mg/dL (70).

Conclusions

GCs have been widely used in minimally invasive interventional pain management due to their anti-inflammatory and analgesic effects. Standard use and compliance with the guidelines above constitute the foundation for ensuring safety and improving efficacy in the use of GCs. Meanwhile, attention should be paid to GCs' associated various adverse reactions, against which active precautionary measures should also be taken.

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