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Safety Implications for Lumbar Epidural Injections: Caudal, Interlaminar, and Transforaminal Approaches

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Abstract Epidural injections of corticosteroids are commonly performed in the United States for pain relief. They can be done via the transforaminal, interlaminar, or caudal route. Each of these routes has a unique risk profile due to the inherent anatomy associated with the procedure. It is imperative that physicians understand these relative risks along with their potential efficacy to best calculate a risk–benefit ratio for a given patient undergoing any procedure. This article will cover the common risks associated with epidural injections, and when available the relative rates of complications depending on route of injection will also be discussed.

Keywords Injections · Epidural · Complications · Safety · Spine · Pain · Adverse events · Interventional pain management · Review

Introduction

Spine pathology is an extraordinarily common problem, with over 25 % of the US adult population reporting back pain in the last 3 months. To help alleviate the suffering from this common condition, physicians can utilize a variety of treatments including exercise, therapies, medications, injections, and even surgery. When considering this large variety of treatment options for patients, physicians must consider the risk-to-benefit ratio for all proposed treatments. To adequately address the benefits of a given treatment, one must review the literature on a disease-specific basis, as low back pain is merely a symptom of a heterogeneous group of conditions. This type of disease-specific evidence-based review has been done before for spine pathologies [1–4], and is thus beyond the scope of this article. Therefore, the purpose of this manuscript is to review the risks and published safety literature for epidural corticosteroid injections in the lumbar spine. Given that lumbar epidural steroid injections (ESI) are done by several different routes including caudal, interlaminar (IL), and transforaminal (TF), this review will also attempt to stratify the relative rates of complications of these varying routes. Additionally to help further guide physicians, the manuscript will differentiate serious complications such as paralysis, spinal infections, and epidural hematoma formation from minor adverse events such as facial flushing and insomnia.

Major Complications

Reported major complications from lumbar epidural steroid injections include paralysis, epidural hematoma, infection, and neural injury. The exact rate of these complications is difficult to ascertain, as the data on these complications mostly reside in case reports. Fortunately, several large cohort studies on consecutive patients have been reported showing no major complications from consecutive subjects. McGrath et al. published the results of 4265 injections on 1857 patients over 7 years detailing 161

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cervical interlaminar injections, 123 lumbar interlaminar injections, 17 caudal injections, and 3964 lumbar TF injections. They identified a lack of major complications and reported 103 minor adverse events, for an overall adverse event rate per injection of 2.4 %. Another review of complications during transforaminal lumbar epidural steroid injections (TFESI) reported the results of a total of 562 patients with 1305 injections, with an overall incidence of minor adverse events of 11.5 %, and no major complications. Botwin et al. evaluated complications of fluoroscopically guided epidural injections by location and approach and noted no major complications, and an incidence of only minor adverse events including headache and increased soreness in 9.6 % of lumbar TF injections and 15.6 % for caudal injections [4, 5].

Recently, several very large multi-institutional studies on complications from interventional procedures have been published [5–7]. These publications came from a cohort of prospectively collected data over many years on consecutive procedures. The procedures were performed by multiple attending physicians, with a variety of specialty training, at several major academic medical institutions including the Mayo Clinic, Northwestern University, and the University of Pennsylvania. This large cohort had over 25,000 consecutive procedures, of which over 16,000 were lumbar transforaminal epidural injections. These manuscripts failed to identify any immediate [5] or delayed [6••] major or permanent complication arising from the procedures, regardless of the route injected [7]. The authors concluded that when performed with rigorous standards [8•], these procedures have a low risk of major complications. Additionally, since these procedures were done at academic training centers, a study was done that demonstrated the only complication that was increased with trainee involvement was temporary vasovagal reactions [9].

Most of our knowledge regarding permanent neurologic complications after epidural injection of corticosteroid arises from animal data, case reports, and extrapolation from other similar medical procedures such as epidural anesthesia for surgical and obstetric procedures. These sources must therefore be placed in proper context for full understanding. Case reports clearly underrepresent the true rate of complications, as the majority of complications are not published in the literature for a large variety of reasons. Conversely, the literature on surgical and obstetric epidural anesthesia may represent a higher risk for some complications such as infection and bleeding. This is due to these procedures typically utilizing an indwelling catheter for the duration of a surgical procedure. Additionally, surgery itself clearly alters body hemodynamics and infection risks, both of which may also contribute to the complication rates with these procedures. Despite these limitations, this information is outlined below to help make physicians aware of potential complications as identified in case reports, while possibly also offering some information of the rates of complications from similar procedures. The remainder of the article will review the literature surrounding the major complications, followed by the data on minor adverse events with a discussion of the effect of the route of epidural utilized when appropriate.

Paralysis

Permanent paralysis has been repeatedly reported in case reports as a complication from lumbar epidural injections [10–16], and has thus generated significant interest from the United States Food and Drug Administration [17] and medical societies [18, 19•]. The generally agreed-upon mechanism for this complication is an infarction due to the inadvertent injection of a particulate corticosteroid into an artery that perfuses the spinal cord [10, 19•]. Particulate corticosteroids have been shown in light microscopy studies to have formations larger than red blood cells [20], or to cause spikulation and aggregation of red blood cells [21], thus explaining the potential embolic nature of these preparations. It has therefore been proposed that the use of non-particulate corticosteroids may eliminate this specific complication [10, 18, 19•, 22], as this complication has never been reported with the use of a non-particulate corticosteroid. In fact, animal studies have demonstrated that the direct intra-arterial injection of non-particulate corticosteroids had no adverse events, while the injection of particulate preparations resulted in clear infarctions [21, 23, 24].

In addition to the use of non-particulate corticosteroids, multiple other safety measures have been proposed to decrease the risk of this particular complication [19•]. These safeguards focus on decreasing the potential of intra-arterial injection or alternatively increasing the ability to detect when such an injection has occurred. Such techniques include the use of digital subtraction technology [25•], the test dosage of an anesthetic agent [26], different needle types [27], as well as potential "safe" needle positions in the foramen [28]. These safeguards have been studied, but given the infrequent nature of this particular complication, it is difficult to determine their true utility in preventing paralysis. However, given the gravity of paralysis, a multi-society work-group did publish numerous consensus recommendations to decrease the likelihood of developing this complication [19•]. These safe guards were agreed upon by experts from 13 medical societies and included the first-line use of a non-particulate corticosteroid as well as the use of real-time fluoroscopy for all epidural procedures that involve the injection of a particulate corticosteroid.

Additionally, the route of injection likely has an influence on the likelihood of developing this particular

complication. Although paralysis has been reported with every approach, including the IL [29, 30], TF [10, 13, 15], and caudal [31], the vast majority of reported cases are via the TF route. This is likely due to the presence of the arteries that supply the spinal cord being within the neural foramen, thereby placing the needle tip in close proximity to the artery. This proximity potentially increases the possibility of inadvertent intra-arterial injection and subsequent paralysis when performing a TF epidural injection.

Infection

By introducing a needle through the skin, all injections have an innate level of risk for subsequent infection. This risk was demonstrated in dramatic fashion in 2012, when there was the largest reported outbreak of fungal meningitis traced back to a source of corticosteroids contaminated with Exserohilum rostratum (*E. rostratum*) from a compounding pharmacy, New England Compounding Center (NECC), in Framington, MA [32]. Doses from these three lots were distributed to 75 medical facilities in 23 states, with doses administered to about 14,000 patients after May 21 and before September 24, 2012. This outbreak alone was linked to at least 64 deaths and more than 720 patients were being treated for persistent fungal infections in 20 states, which has led to active debates regarding the use of compounding pharmacies [33]. Most of these infections were in people that underwent spine procedures for pain.

Prior to this massive incident, infectious complications following epidural injections were felt to be rare, with the majority of reported cases being single cases or small case series. The infections varied in severity from minor colonization of a local skin infection to epidural abscess or even meningitis. To date, the serious infectious complications following epidural steroid injections reported in the literature include three cases of epidural abscess, one case of bacterial meningitis, and one case of aseptic meningitis [34–37]. No cases of spinal infection have been demonstrated in large cohorts of patients receiving epidural steroid injections [38]; however, there are data available from several large studies of patients that had epidural anesthesia for surgical or obstetric purposes. A large retrospective review of patients having spinal anesthesia found 3 cases of post-spinal meningitis in 38,128 spinal anesthetics, compared to no cases in 12,822 patients that received peripheral or general anesthesia [39], while another large review of nearly 50,000 patients that received epidural anesthetics found no epidural or intrathecal infections [39]. A multicenter prospective study including 40,640 spinal and 30,413 epidural anesthetics also did not report any infection complications [40]. The largest cohort to date by Aromaa et al. reported 8 cases of bacterial infection to the spine or central nervous system (CNS) after 170,000 epidural and 550,000 spinal anesthetics, for an overall frequency of 1.1 per 100,000 blocks [41••]. These data do offer additional insights, but as noted above they may not be fully representative of epidural steroid injections.

The clinical course of epidural abscess progresses from spinal ache and root pain to weakness including bowel and bladder symptoms and may progress to paralysis. The initial symptoms of an infection are typically increased back and radicular pain. Spinal infections can be exceedingly difficult to diagnose given that the symptoms may be stable or slowly progressive for weeks. However, once the patient has an onset of weakness, they may progress to complete paralysis within 24 h. Therefore, a delay in diagnosis and treatment of spinal infections may significantly worsen the neurologic outcome. All patients with fever, local or systemic infection should be considered to be at risk for developing a CNS infection. Additionally, there are several risk factors for infections in patients that should be noted including underlying sepsis, diabetes, depressed immune status, chronic steroid therapy, localized bacterial colonization, ongoing infection, and chronic catheter maintenance.

Historically, the diagnosis was made with myelography; however, the current recommendations are either CT or MRI. If meningitis is suspected, the diagnosis can be confirmed with a lumbar puncture with leukocytosis, a glucose level of <30 mg/dL, and a protein level >150 mg/dL. However, a lumbar puncture should not be performed if an epidural abscess is suspected, because it may result in the contamination of the intrathecal space. Abscess formation can be superficial and can be treated with IV antibiotics and limited surgical drainage. However, an abscess deep in the epidural space can cause spinal cord compression and thus may require aggressive early surgical management to prevent serious neurologic injury [42, 43]. Neurologic recovery is dependent on the duration of the deficit and severity of neurologic impairment prior to the initiation of treatment [39, 40]. Bacterial and fungal meningitis are a medical emergency and typically require hospitalization with intravenous antibiotics. Unfortunately, even with appropriate treatment the mortality of bacterial meningitis is approximately 30 %.

Epidural Hematoma

Given the nature of an injection, localized bleeding is universal. The concerning hematologic complication from an epidural injection is the development of an epidural hematoma. Similar to paralysis and infection, several large cohorts of consecutive patients exist that all have failed to show the development of an epidural hematoma after an epidural injection [5–7]. Another cohort of 10,000 patients found that 0.21 % (14 of 6745) of patients had bruising at

the site, 0.13 % (9 of 6745) had a local subcutaneous hematoma, and no patients developed an epidural hematoma [41••]. Another smaller prospective study of 1035 individuals undergoing 1214 epidural steroid injections by Horlocker et al. found that only 5.2 % of patients had minor bleeding at the skin during needle placement, and no patients developed a spinal hematoma [44•]. Interestingly, this study population consisted of 185 individuals (17.9 %) on aspirin therapy and 176 patients (17 %) with a history of bleeding or bruising, and yet they still had the low rates of hematologic issues and no major complications. Moreover, they concluded that NSAIDs, including aspirin, did not seem to increase the risk of hematologic complications [44•].

Despite the existence of several large cohorts of patients receiving spine injections for pain, thus far epidural hematomas have only been reported via case reports for patients having epidural injections for spine pain. The lack of data makes it challenging to determine a true rate of this complication; however, the literature on epidural hematomas following spinal anesthesia for surgical procedures and obstetrics has shown this to be a rare complication, and typically limited to those mostly related in epidural anesthesia with full anticoagulation [44•].

The risk of epidural hematoma formation likely varies based on the route of injection. To date, all of the reported hematomas in the literature occured following the IL route, aside from one case report via the TF route. Additionally, the single reported case of an epidural hematoma following a TF injection was not at the same location as the injection. Given that epidural hematomas can develop spontaneously, and the injection was not near the reported hematoma, it is likely that the hematoma was not causally related to the procedure. Therefore, this complication appears to be mostly secondary to the IL approach.

In addition to the route of injection, anticoagulation medications would clearly have an effect on the possibility of developing a hematoma. There are published guidelines detailing suggested time frames to stop anticoagulation medications [44•]; however, there is still debate over the relative risk of stopping these medications [45]. Specifically, physicians must weight the risks of a hematoma formation versus the risks of developing an embolic complication from stopping these prescribed medications. This risk-to-benefit ratio should be done on an individual basis taking into account multiple factors including risks of the procedure, benefit of the procedure, risks of alternative treatments, and risks of stopping the medications.

Direct Neural Injury

Neurologic complications can occur due to an intra-neural injection; however, direct needle trauma alone has no reported cases of permanent neurologic injury. All the reported cases of permanent neurologic deficits have occurred only after an injection of a solution. The reported cases in the literature have been confined to direct spinal cord injection following thoracic or cervical IL ESI [6••, 7]. No cases of direct neural injury have been reported following a lumbar injection or a TF ESI. The lack of cases in the lumbar spine is probably due to the fact that the spinal cord typically terminates at the L2 level, and therefore the only plausible mechanism of direct lumbar spinal cord injury in a person with normal anatomy would be from an IL ESI at the L2 level or higher. It is not surprising that this complication has not been reported given that the majority of spine pathology occurs at the L4 to S1 levels. There are also clear safety measures that if followed would eliminate this particular risk. Specifically, physicians must utilize a depth view (either a lateral or contra-lateral oblique) when preforming IL injections prior to injecting the injectate [8•]. By doing this simple and essential task, the physician could rapidly recognize that the needle tip is beyond the target and could withdraw the needle prior to injection.

Minor Adverse Events

Minor adverse events are transient in nature without permanent sequela. The commonly reported adverse events include vasovagal reactions, fascial flushing, increased pain, changes in blood glucose, minor bleeding such as bruising, dural punctures, headaches, and allergic reactions. These types of adverse events are much more than the aforementioned major complications, and have documented rates as demonstrated by large cohorts. McGrath et al. published the results of 4265 injections over 7 years and noted an overall adverse event rate per injection of 2.4 % [46••]. Another study on 1305 injections found a much higher rate of minor adverse events at 11.5 % [47]. The most common complication shown is typically headache and increased soreness, with the highest reported rates being 9.6 % for lumbar TF injections and 15.6 % for caudal injections [38, 48]. The overall variance between the rates of adverse events reported in these studies is likely due to time frame for follow-up, method of data acquisition, and definitions of complications. Studies that had rigorous independent nursing follow-up close to the procedure likely had less recall bias [5, 7, 39, 48]. The remainder of this article will review the specific literature surrounding the more common adverse events.

Transient Increased Pain

Increased pain can occur whenever the skin is penetrated by a sharp object. Often, a small bore needle (27 gauge) is

inserted percutaneously to anesthetize the skin and subcutaneous tissues to decrease pain resulting from insertion of the spinal needle. The acidity of the anesthetic agent could also cause a discomforting "sting" to the patient; however, the basic sodium bicarbonate whose addition has been shown to decrease this sting can be used as a buffering agent [49–51].

Furthermore, patients may report soreness at the injection site hours after the procedure after the local anesthetic has worn off, though this is usually self-limiting. Additionally, direct irritation from the injectate or trauma to the nerve from the spinal needle can produce discomfort that may exacerbate or replicate the patient's pain. The relay of this information from the patient to the physician during the procedure may be a signal that the needle is approaching or impacting the exiting nerve root or the spinal cord and provide the physician a chance to readjust the needle. This feedback allows the clinician to reposition the needle, and it is for this reason that deep sedation is ill-advised. Transient nerve root irritation is not uncommon and has been reported to vary based on route of injection. Manchikanti noted an incidence of 0.28 % of interlaminar, 0.0 % of caudal, and 4.6 % of TF injections for a total of 0.95 % (64 of 6745) for all lumbar ESI [52••].

Vasovagal Reactions

Vasovagal reactions can occur in any injection and depending on the severity of the patients' symptoms and response to intra-procedural treatment may require the procedure to be aborted. An extensive review of 10,000 epidurals reported that only 1 of 6745 lumbar interlaminar, TF, or caudal injections resulted in a vasovagal reaction (0.01 %) [53]. This is significantly lower than those reported in other studies and may suggest a reporting bias. Kennedy et al. reviewed 8000 procedures and found the overall rate of vasovagal reaction to be 2.6 % for all fluoroscopically guided injections, and a rate of 3.5 % for lumbar TF injections, 1.6 % for caudal injections, and 0.7 % for interlaminar injections [22]. However, although they found that a number of cases needed to be aborted, no further intervention with intravenous hydration or hospitalization was required and all the patients were able to return home. Additionally, patients may be at risk after the procedure for orthostatic hypotension due to the vasovagal reaction. Frequently, this can be easily remedied in clinical practice by having the patient placed in Trendelenberg position or having patient slowly go from lying to sitting before attempting to stand and ambulate. Rarely, there is a need for intravenous fluid administration. No significant differences in vasovagal rates existed between injection routes.

Dural Puncture

Dural puncture is a relatively common complication typically associated with IL epidural injections, and is the most common post-procedural complication of the neuraxis. Inadvertent spinal dural puncture during epidural injections can occur with subsequent entry into the subdural and subarachnoid space. Dural puncture can occur with an interlaminar approach when the needle is advanced beyond the dorsal epidural space, thereby entering the central spinal canal. Dural puncture can also occur with the TF approach via penetration of the dural sleeve that surrounds the exiting spinal nerves, although this occurs infrequently. Cerebral spinal fluid (CSF) flashback is typically the first sign used to recognize the complication of a dural puncture. Additionally, recognition of epidural contrast spread versus subdural and subarachnoid contrast spread patterns is essential because dural penetration may not be accompanied by CSF flashback alone [52••]. The overall incidence of dural punctures in epidurals ranges from 0.5 to 0.8 % of interlaminar injections [52••]. Risk factors for dural puncture include previous surgery in area of needle placement, calcified ligaments, obesity, and patient movement. Technique also plays a role with a higher rate of dural puncture occurring with the midline approach, steep needle angle, and the use of an introducer needle. Also for the caudal approach, the needle should not be advanced cephalad to S2 given the thecal sac ends at this level, thus allowing physicians to easily avoid inadvertent intrathecal injection.

The most commonly reported sequela associated with inadvertent dural puncture is a post-dural headache. Post-dural headaches are typically severe, dull, non-throbbing pain, and fronto-occipital in location, which aggravate in the upright position and diminish in the supine position. CSF can leak through the dural puncture leading to a loss of CSF pressure and a drop in brain volume. Prevention of dural puncture complications such as post-dural headache begins with identifying the known risk factors and utilizing the best technique with the smallest non-cutting needle. Once accidental dural puncture is recognized, it may be possible to reduce the risk of developing post-dural headaches by injecting 10 ml of preservative-free normal saline before removing the needle [53].

Additionally, patients should be informed of the dural puncture through a straightforward explanation of the etiology, natural history, and treatment options for potential post-dural headache. Reassurance and explanation of supportive measures should be provided to the patient. The patient should be advised about the postural nature of the headaches, and how a recumbent position provides therapeutic relief. The patient should be counseled to increase oral fluid intact to prevent worsening symptoms with dehydration

[52••–55]. Caffeine intake has been used both orally and intravenously with published studies consistently demonstrating an improvement of headache symptoms at 1–4 h in over 70 % of patients and particularly after receiving fluids with caffeine [56, 57, 60]. In addition to utilizing immediate injection of normal saline into the epidural space, an epidural blood patch (EBP) can also be utilized and has increased in popularity over the past several decades. The epidural blood patch procedure has been well described and consists of a sterile injection of autologous blood at or below the level of previous dural puncture due to the preferential cephalad spread of blood in the epidural space [58]. The proposed mechanism of EBP is the ability to stop further CSF loss by the formation of a clot over the defect in the meninges as well as a tamponade effect with cephalad displacement of the CSF. [8•, 59] Overall, post-dural headaches respond well to a combination of these treatment options and symptoms abate without any long-term sequela.

Adverse Systemic Effects of Corticosteroids

Corticosteroid therapy has well-documented adverse effects whether they are used in short or long term. These adverse effects include systemic changes such glucose intolerance, hypokalemia, hypertension, pancreatitis, hyperlipidemia, and adrenal insufficiency. Musculoskeletal side effects of corticosteroids include myopathy, osteoporosis, and avascular necrosis of the femoral and humeral heads. There are many neurologic and side effects such as psychosis, dementia, seizures, benign intracranial hypertension, increased ocular pressure, and cataracts. Additionally, there are many dermatologic adverse effects such as weight gain, truncal obesity, hirsutism, and cutaneous changes. In a study by Moon et al. on 14 subjects, seven of which had pre-existing diabetes, it was found that blood glucose levels were increased at 1 and 7 days after a corticosteroid injection in the epidural space, but the levels had returned to baseline at 21 days [74]. The average increase in fasting blood glucose increased by an average of 20 points, and peaked at post injection day #1. The authors suggested that diabetics take more time between injections.

Overall, it is clear from the review of the literature that the administration of corticosteroids via lumbar epidural injections causes a transient adrenal suppression that resolves within a month of the injection.

Hypercorticism/Adrenal Suppression

The administration of exogenous corticosteroids has a direct effect on the entire hypothalamic–pituitary–adrenal axis. Notably, Cushingoid syndrome is an iatrogenic adrenal insufficiency secondary to prolonged exogenous administration of glucocorticoids. Prolonged lack of cortisol can lead to severe fatigue, chronic exhaustion, depression, loss of appetite, and weight loss. Whereas decreased levels of aldosterone can lead to decreases in blood pressure, they potentially increase the frequency of orthostatic hypotension. Loss of dehydroepiandrosterone (DHEA) production by the adrenals can result in a loss of pubic and underarm hair and also potentially reduced sex drive and low energy levels.

Cushingoid syndrome leads to a constellation of other symptoms as well including weight gain, abnormal fatty tissue deposits known as moon faces and buffalo hump, purple striae on the skin of the trunk and appendages, ecchymosis, and hirsutism. There are also sexual/reproductive symptoms such as irregular or absent menstrual periods, decreased libido, decreased fertility, and erectile dysfunction. Additionally, this secondary hypercorticism may lead to osteoporosis and steroid myopathy [60–63].

Cushingoid effects of epidural administration of corticosteroids have been demonstrated in numerous studies [64–69]. The active corticosteroid is slowly released over a period of days to 1–3 weeks; however, it is most common for the patients to repeat side effects in the first three post treatment days. The typical Cushingoid symptoms start to develop several weeks after the injection, and typically resolve within a month. However, there was a case report of a patient who underwent 3 stellate ganglion blocks followed by a cervical epidural within a month leading to Cushingoid symptoms that lasted a year [69]. Post injection laboratory evaluations have demonstrated significant depression of plasma cortisol and ACTH as early as 45 min after the injection, and remaining reduced for 21 days. Additionally, the administration of exogenous ACTH to increase plasma cortisol was also reduced. However, these levels normalized at 30 days after the last injection [49, 70–73]. Another study evaluating salivary cortisol levels following epidural injections revealed that there was hypothalamus–pituitary–adrenal (HPA) axis suppression until day 21 and returned to the normal range after 19.9 ± 6.8 days. These authors suggested that there should be an interval between epidural steroid injections of at least 1 month [74]. Overall, it is clear from the review of the literature that the administration of corticosteroids via lumbar epidural injections causes an immediate suppression that typically resolves between 21 days and 1 month. Since the most severe cases of adrenal suppression are following multiple injections, it is recommended to avoid planned series of injections [75, 76].

Conclusions

Lumbar epidural steroid injections have known major complications including paralysis, infection, and epidural hematomas. These complications are rare and only reported

in case reports. Despite this low risk, patients should be counseled as to the potential of these risks prior to the procedure. Additionally, safety protocols should be followed to decrease the risk of peri-procedural complications, including the use of a time-out for site verification. During the procedure, the physician should exercise necessary caution in needle placement, and be able to recognize concerning dye flow patterns. Additionally, the physician must be aware of signs and symptoms of the various complications and be prepared to act immediately to address these issues. With proper management, these major complications should be minimized and the patient will only be subjected to the potential of minor adverse events.

Compliance with Ethics Guidelines

Conflict of Interest Arthur Jason De Luigi and David J. Kennedy declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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