

Focused Review

Steroid Distancing in Interventional Pain Management During COVID-19 and Beyond: Safe, Effective and Practical Approach

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Background: Since the late 1940s, corticosteroids have been a mainstay class of agents in multiple interventional techniques and intra-articular injections. Exogenous glucocorticoids are structurally and pharmacologically similar to the endogenous hormones. As such, multiple actions of corticosteroids are exhibited, including those of anti-inflammatory and immunosuppressive effects. Epidural injections, with or without steroids, have been extensively used throughout the world. There are reports of epidural injections starting in 1901, with steroids being added to the local anesthetic since 1952, when steroids were administered into the sacral foramen.

Purpose: Due to the extensive side effects of steroids in various injections, some have proposed limiting their use in epidurals and intraarticular injections. With the COVID-19 pandemic, the multiple side effects of the steroids have elevated the level of concern and recommendations have been made to utilize local anesthetic alone or the lowest dose of steroids. Fashioned from common expressions of the day, the term “steroid distancing” began to be used and proposed for intraarticular injections of the knee. Consequently, we sought to evaluate the evidence and feasibility of steroid distancing in interventional pain management.

Methods: This focused review of local anesthetics and steroids utilized in interventional pain management for epidural injections, peripheral nerve blocks, and intraarticular injections by multiple database searches. This is a focused narrative review and not a systematic review. Consequently, evidence synthesis was not performed traditionally, but was based on an overview of the available evidence.

Results: No significant difference was identified based on whether steroids are added to local anesthetic or not for epidural as well as facet joint injections. However, there was not enough evidence to compare these 2 groups for peripheral intraarticular injections.

Limitations: The present review is limited by the paucity of literature with bupivacaine alone or bupivacaine with steroids local anesthetic alone or with steroids of intraarticular injections of knee, hip, shoulder and other joints, and intraarticular facet joint injections.

Conclusion: This review shows an overall lack of significant difference between lidocaine alone and lidocaine with steroids in epidural injections. However, available evidence is limited for bupivacaine alone or with steroids. Evidence is also not available comparing local anesthetic alone with steroids for facet joint or peripheral joint intraarticular injections. Thus, it is concluded that local anesthetic with lidocaine may be utilized for epidural injections, with appropriate patient selection and steroids reserved for non-responsive patients with local anesthetic and with significant radiculitis.

Key words: Steroid distancing, chronic pain, steroids, epidural injections, local anesthetic alone, local anesthetic with steroid, steroid distancing, physical distancing

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1.0 INTRODUCTION

Corticosteroids have been one of the most commonly used or mainstay classes of agents in epidural injections, peripheral nerve blocks, and intraarticular injections and this use started soon after their introduction into clinical medicine. Corticosteroids are hormone mediators produced by the cortex of the adrenal glands that are further categorized into glucocorticoids (major glucocorticoid produced in the body is cortisol), mineralocorticoid (major mineralocorticoid produced in the body is aldosterone), and androgenic sex hormones (1). Endogenous cortisone was first isolated in 1935 and synthesized in 1944 (1). In 1948, Philip S. Hench administered cortisone, which was called compound E at that time, to a 29-year old woman who was bedridden secondary to active rheumatoid arthritis and reported the ability of the patient to walk after 3 days of treatment. Hench published this case report in 1949, and in 1950, Hench and others (2-5) were awarded the Nobel Prize in physiology or medicine for "their discoveries relating to the hormones of the adrenal cortex, their structure, and biologic effects" (2). Hench et al also published their landmark study in 1950 in JAMA (3). Following this introduction of steroids into epidural injections, in 1952 and 1953 (6,7), they introduced it for intraarticular injections (4), and subsequently, they published multiple manuscripts in relation to administration of corticosteroids for inflammatory conditions (2-25).

Glucocorticoids are structurally and pharmacologically similar to the endogenous hormone, cortisol. Like cortisol, they have immunosuppressive, anti-proliferative, vasoconstrictive anti-inflammatory effects, which is the common denominator for utilizing them in neural blockade (1-3,6-10). The anti-inflammatory and immunosuppressive effects of glucocorticoids are dose dependent, with immunosuppressive effects seen mostly at higher doses (1). The majority of effects produced by glucocorticoids results from connecting to intracellular receptors with subsequent translocation to the cell nucleus leading to activation of anti-inflammatory proteins and repression of proinflammatory proteins. The literature shows that most effects of glucocorticoids are through the genomic mechanisms, which is of slow onset, while immediate effects are through non-genomic mechanisms with high doses of glucocorticoids.

While epidural steroid injections have been extensively used throughout the world since 1952 (6-10,26). The initial use and assessment of intraarticular

steroid injections for facet joint pain was reported by Mooney and Robertson in 1976 (8). However, their introduction and continued utilization in spine has been associated with discordant opinions (6-19,26-31), along with complications (32-35). In fact, attempts even have been made to severely restrict or remove steroids from epidural administration (35,36). In addition, safeguards also have been described to prevent neurological complications after epidural steroid injection with 17 items (35). The Food and Drug Administration (FDA), continued to retain the warning about epidural steroid injections that they are associated with significant complications. Efforts by the American Society of Interventional Pain Physicians (ASIPP) led these safeguards (36) to remain as guidelines that were not specifically adopted by the FDA (37).

Historically, steroids were not the first substances to be reported as effective pain interventions in any type of neural blockade, including epidural injections or intraarticular injections (6-10,12). In 1901 Sicard (38), known as the first pain doctor, and Pasquier and Leri (39), also in 1901, for anesthetic treatment of low back and lower extremity pain. Cathelin (40) one week later in 1901 reported anesthesia and pain relief of inoperable cancer of the rectum. Subsequently, reports on cures of sciatica with epidural anesthesia were published prior to the availability of steroids by Caussade and Queste (41). Evans (42) in 1931 published a successful report using procaine and saline in 22 of 40 patients. Cyriax published a series of manuscripts (43,44) referring to safe use of caudal epidural injections using only local anesthetic in more than 20,000 cases.

Due to extensive use of steroids for multiple ailments, the case for and against corticosteroid distancing in the management of knee osteoarthritis published in May 2020, interestingly, without mentioning COVID-19 or social distancing (45). This publication included a survey of physicians in reference to corticosteroid distancing and their concerns. This article came into a substrate of rigorous research into the effect of local anesthetic alone or local anesthetic with steroids, specifically with lidocaine for epidural injections, along with a few studies with bupivacaine and bupivacaine for nerve blocks (12-25,30,31,46-48). These manuscripts with analysis of evidence from randomized controlled trials (RCTs) have shown a lack of significant difference between using local anesthetics alone or in combination with steroids. Further, no significant difference was identified between sodium

chloride solution alone or with steroids (15).

Returning to the present situation related to COVID-19, the public is attempting to return to work and activities with near normalcy (49-54). Emerging from this crisis America is opening its doors for patient care. Consequently, multiple manuscripts have been published (49-54) describing economic recovery aspects with resumption of near normal healthcare, including interventional pain management practices. Shah et al (52) provided risk mitigation/stratification strategies to return to work with recommendations to perform the procedures with local anesthetic alone, or use the lowest dose of steroids. Logically, clinicians practicing in the COVID era are faced with the challenge of how to perform interventional pain procedures with sustainable effectiveness and whether a lower dose of steroid (or avoidance of steroid altogether) is a possibility (25,30,31,46-48,55-69). Consequently, this focused narrative review was undertaken to provide recommendations on "steroid distancing," a term coined by Mundi et al (45).

2.0 METHODS

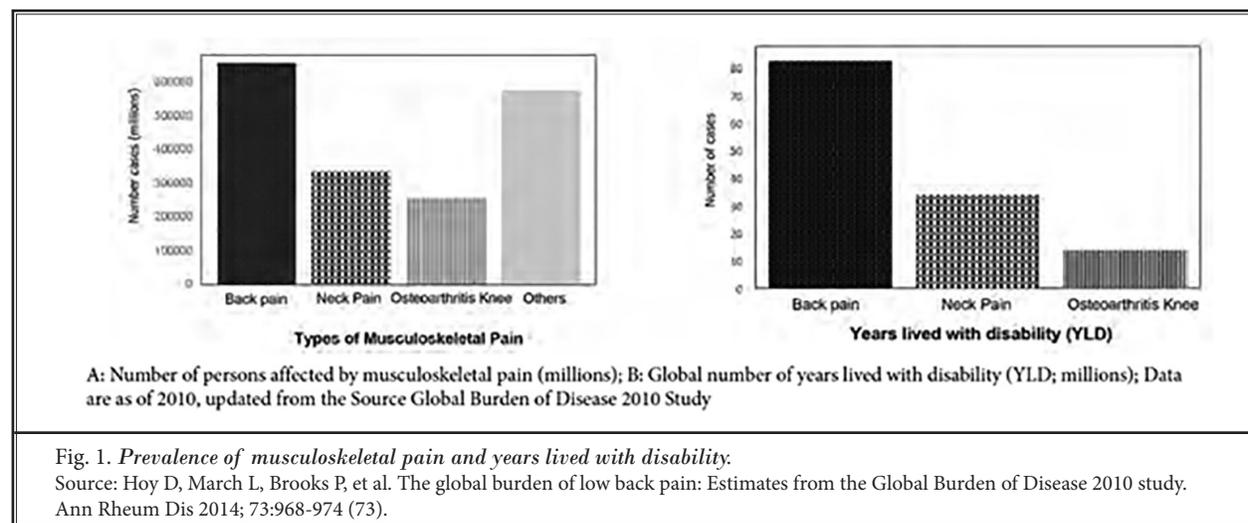
This focused, narrative review utilized simple methodology with a literature search from multiple databases. However, evidence based synthesis of the literature was not carried out. Thus, the derived results are based on a focused, narrative review of the literature.

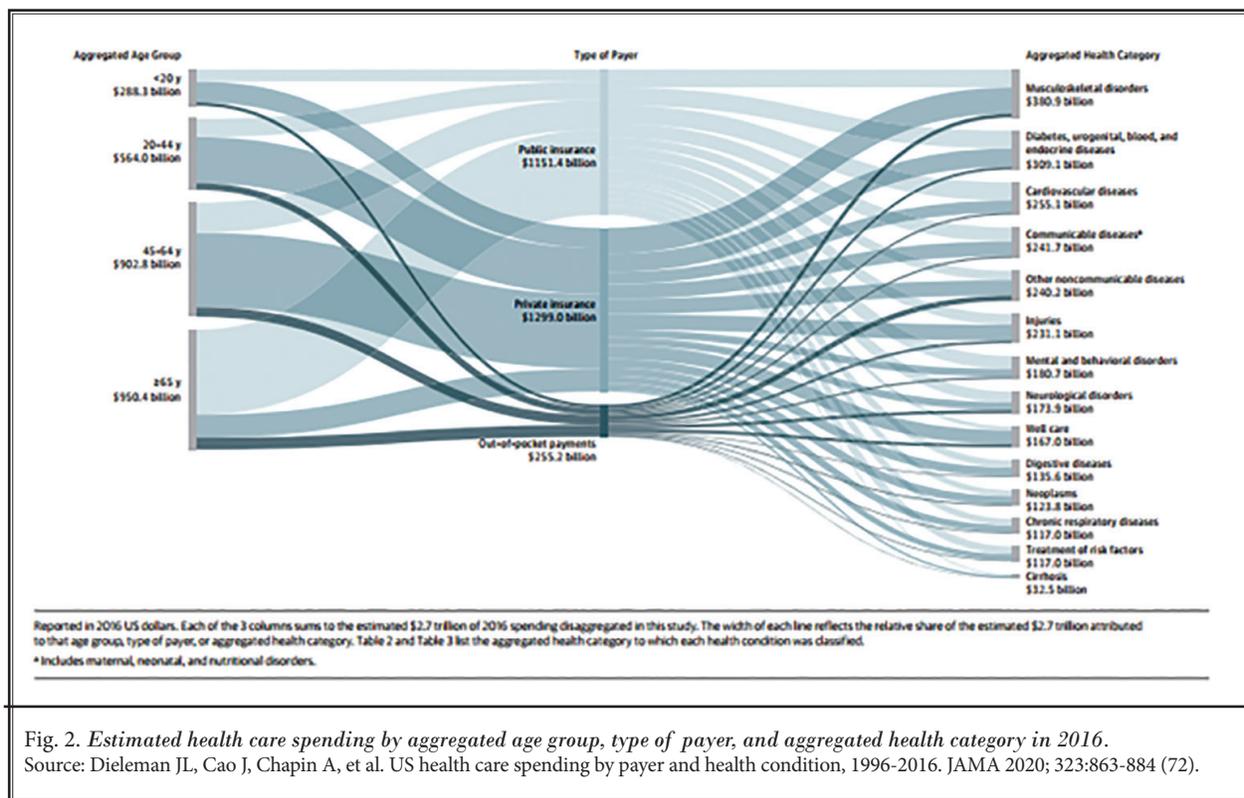
3.0 RESULTS

3.1 Neural Blockade and Injection Therapy for Chronic Pain

The impact of chronic pain on health, health care, and the economy (30,55,70-72) is enormous. Dieleman et al (72) assessed US spending on person and public health care from 1996 to 2016 showing ominous data in reference to the expenditures increasing health care spending from an estimated \$1.4 trillion in 1996 or \$5,259 per person with 13.3% gross domestic product (GDP) to an estimated \$3.1 trillion in 2016 with an estimated GDP of 17.9% and per person costs of \$9,655. Further, in 2016, a total of \$264.3 billion were spent on musculoskeletal disorders and spinal pain with a 44.4% increase compared to 2013. Figure 1 shows prevalence of musculoskeletal pain and years lived with disability (73), whereas Fig. 2 shows expenditures on health care secondary to various disorders including musculoskeletal including osteoarthritis and spinal pain (18-24,70-72).

Multiple modalities in managing chronic musculoskeletal pain, including spinal pain, have been employed including over the counter drugs, exercise programs, physical therapy, opioids, rehabilitation programs, interventional techniques utilizing neural blockade and intraarticular injections with or without steroids, and surgical interventions (70-72,74).





Chronic pain involves complex biostructural and biopsychosocial mechanisms. For neuraxial pain, epidural injections, facet joint interventions, sacroiliac joint interventions and percutaneous adhesiolysis, along with other minimally invasive procedures and for osteoarthritis, intraarticular injections are the most commonly utilized modalities.

The use of interventional techniques for the treatment of spinal pain and musculoskeletal disorders escalated until 2009, at which point utilization started decreasing from previous years (74). Overall, the tendencies are declining utilization for almost all of interventional techniques. Figure 3 shows distribution of procedural characteristics by type of procedures from 2000 to 2018.

In addition, nerve blocks and intraarticular injections are common for knee (21-23,45,75,76), shoulder (77-79), hip (80-83), multiple other joints (84), carpal tunnel (85), nerve blocks for suprascapular nerve (86-88), intercostal nerve block (89-91), sympathetic blocks (92,93), tendinous and trigger point injections (94).

In neural blockade, the rationale for injecting local anesthetic is to block sensory signals. Even though

they are often used for diagnostic purposes and believed to provide a temporary effect, due to the decrease in sensitization and various other mechanisms, they may produce long-term relief very much beyond its pharmacological duration of action (15-19). In clinical practice, steroids are typically combined with local anesthetic, with hopes of prolonging the relief (9-19,95,96). However, with the COVID epidemic, apart from the anti-inflammatory effects of steroids, but also immunosuppressive effects and related complications have been brought into focus.

The rationale for neuraxial steroid use is primarily based on the benefits of neural blockade, which include pain relief that outlasts by hours, days, and sometimes weeks, the transient pharmacologic actions of other adjuvant agents such as local anesthetics; however, despite such explanations they continue to be an enigma. Neural blockade effectiveness is based on the postulation that it alters or interrupts nociceptive input, reflex mechanism of the afferent limb, self-sustaining activity of the neuronal pools in the neuroaxis, and the pattern of central neuronal activities (9-19). Consequently, pharmacological and physical

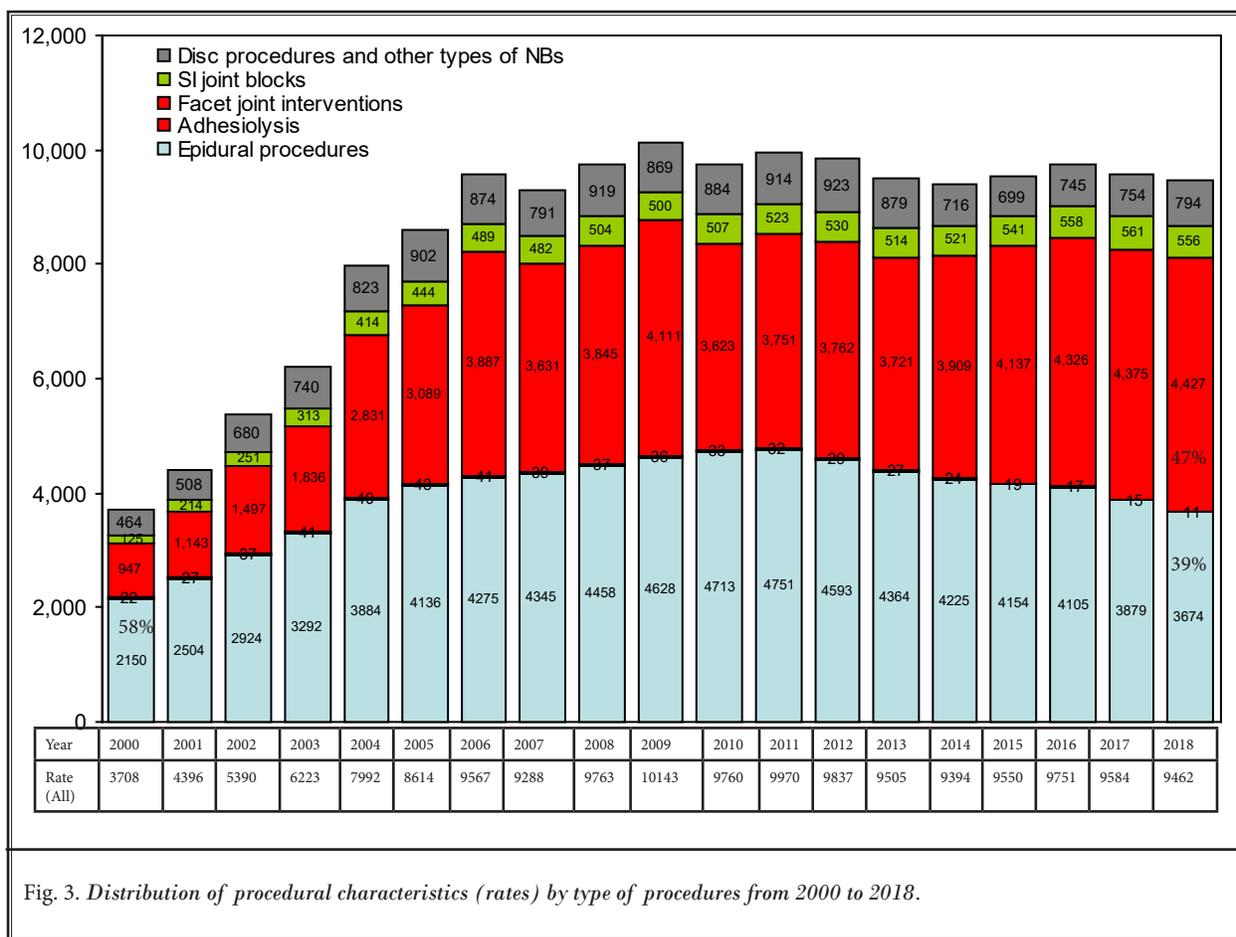


Fig. 3. Distribution of procedural characteristics (rates) by type of procedures from 2000 to 2018.

actions of corticosteroids, along with local anesthetics have been the basis of such explanations.

Intraarticular injections have been performed for various types of arthritis into almost all types of joints (1-5,20-25,76). However, knee injections have been the most commonly performed procedures. Clinical use of intraarticular injections dates back to 1930s when formalin, glycerin, lipodil, lactic acid, and petroleum jelly were among the first substances injected into patients with arthritis. Now corticosteroids and hyaluronate preparations constitute the mainstay of the FDA-approved intraarticular therapeutics (12,20,76). Multiple RCTs, systematic reviews, and other types of reviews have described discordant opinions for corticosteroid injections (9-27,44,76).

3.2 Steroids in Chronic Pain: Mechanism of Action

Corticosteroids in neuraxial blockade have been

postulated to reduce inflammation, either by inhibiting the synthesis or release of a number of proinflammatory substances or by causing reversible local anesthetic effect (1,9-18). Multiple modes of action of corticosteroids include membrane stabilization, inhibition of neural peptide synthesis or action, blockade of phospholipase A2 activity, local anesthetic effect, prolonged suppression of ongoing neuronal discharge, and suppression of sensitization of dorsal-horn neurons (1,7,9-18). However, there is no evidence that steroid injections are disease-modifying agents with direct effect on pain generation or transmission with an exception of inflammatory conditions such as rheumatoid arthritis. Further, there are no studies demonstrating the anti-inflammatory role of steroids or differentiation of inflammatory radiculopathies from noninflammatory radiculopathies (7,9,10-18). During the search for confirmation of the anti-inflammatory effect of steroids in epidural injections, multiple

explanations relied an inflammatory component in lumbosacral radiculopathy. The first evidence suggesting inflammation in patients with radiculopathy was published in 1981 (29). Ryan and Taylor (29) examined samples of cerebral spinal fluid during administration of intrathecal and epidural injections, and theorized that inflammation was a critical component of radicular pain, and that intraspinal steroids were likely to be most effective when this inflammation was still acute, before the pathology had progressed to nerve root fibrosis or axonal death. This led to the classification of 2 categories of radiculopathy, compressive and irritative.

Epidural injections of betamethasone in a model of lumbar radiculopathy showed a significant effect on thermal hyperalgesia, while administration of intravenous methylprednisolone significantly reduced the nerve root injury produced by epidural application of autologous nucleus pulposus in a pig experimental model (97-101). Another study concluded that lipopolysaccharide accelerated the process of herniated intervertebral disc resorption, whereas high-dose steroids suppressed the process (102). A publication studying the effect of local methylprednisolone on pain in a nerve injury model by inducing peripheral mononeuropathy showed that the heat hyperalgesia and mechano-allodynia, but not mechano-hyperalgesia were depressed in the animals receiving corticosteroids; however, not in those treated with saline, with the effect remaining during the 11 day test period (103). The effects of systemic methylprednisolone on acute nociception and on pain behavior in hyperalgesia were studied in normal and neuropathic rats (104). The results showed that chronic steroid treatment prevented the development of neuropathic edema and completely blocked neurogenic extravasation; however, the findings also showed that corticosteroids did not affect nociceptive thresholds in normal or neuropathic hyperalgesic rats.

Ever since the descriptions of Hollander et al (105) in 1951, enthusiasm erupted with temporary improvement of symptoms in many cases, but it was also tempered by warnings of the possibility of increasing the damage in joints subjected to excessive use in periods of freedom from symptoms. Their early publication in 1951 (5) also noted that the results of treatment of the knee have been more encouraging than those of treatment of other joints, presumably because of the ease with which injection of the knee joint can be accomplished. Evans et al (25) described that diarthro-

dial joints are well suited with regard to intraarticular injection, and the local delivery of therapeutics in this fashion brings several potential advantages to the treatment of a wide range of arthropathies. They described potential benefits including increased bio-availability, reduced systemic exposure, fewer adverse events, and lower total drug costs. Prior to the advent of TNF antagonists, intraarticular corticosteroid injections into all joints was one of the important modes of therapy for rheumatoid arthritis (4). This importance continues in osteoarthritis and traumatic arthritis. The major motivation for intraarticular delivery of corticosteroids has been to increase effective dosing.

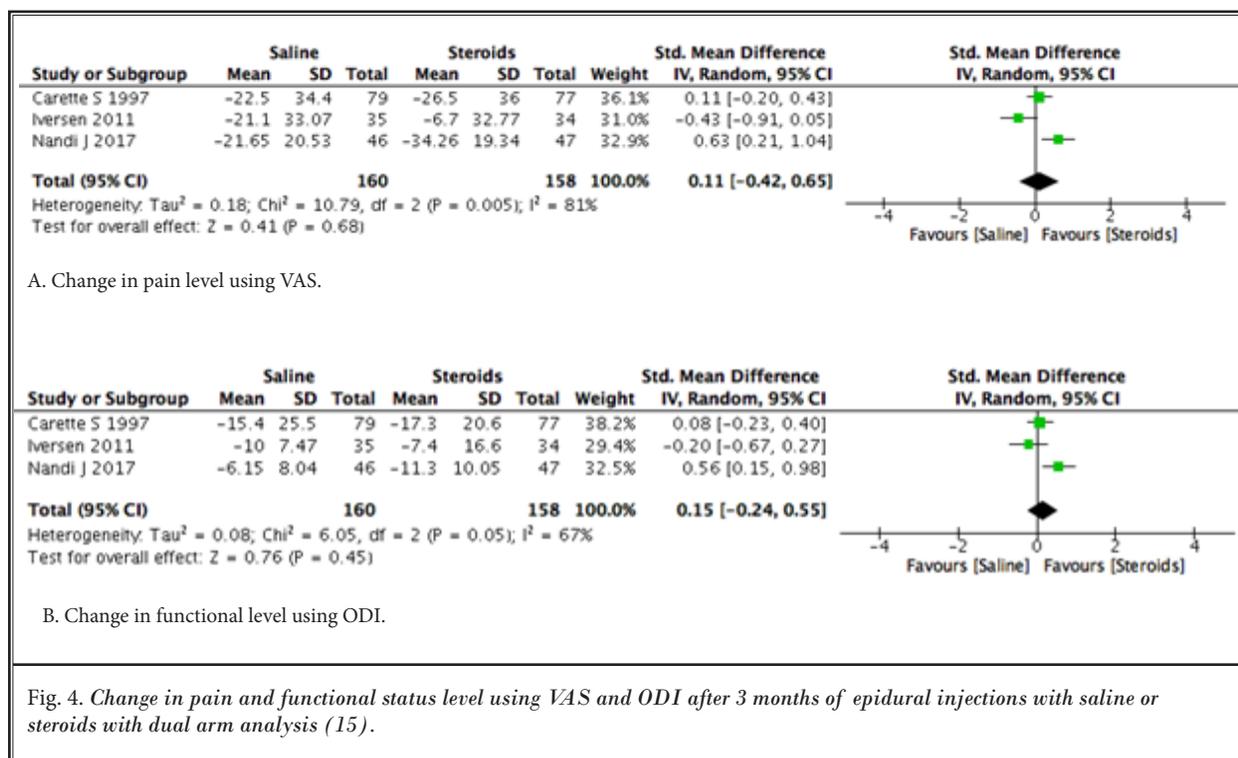
3.3 Local Anesthetics in Chronic Pain: Mechanism of Action

Local anesthetics have been used ever since the discovery of the medicinal properties of cocaine, long before the compound was brought to Europe for its local anesthetic properties to be discovered (12,15,17,18). Based on this foundation, regional anesthesia developed into interventional pain management. In 1899, Tuffer (106) described therapeutic nerve blocks in pain management using spinal injections of cocaine to control pain from sarcoma of the leg. In 1903, Cushing described pain relief with nerve blocks (107), along with reports of trigeminal alcohol blockade (108).

Development of caudal epidural injections for pain management began in 1901 (38-41) and interlaminar epidural injections in 1933 by Dogliotti (109).

John Bonica vigorously nurtured interest in pain medicine (110). Local anesthetics have been used in many nerve block clinics in operation by the 1950's. Local anesthetics were used exclusively until 1951 when steroids were identified and came into use (2-7,10,12,23).

The effectiveness of local anesthetics in chronic pain is based on anti-inflammatory actions (12,13,15,17,18) and the alteration of multiple pathophysiologic mechanisms including noxious peripheral stimulation, excess nociception resulting in the sensitization of the pain pathways, and excess release of neurotransmitters causing complex central responses including hyperalgesia or wind-up, resulting in an increase in nociceptive sensitization of the nervous system, and phenotype changes which are also considered as part of the neuronal plasticity. Sato et al (111) showed the prolonged analgesic effect of epidural ropivacaine in a rat model of neuropathic pain. On the



same token Tachihara et al (112) provided evidence that there is a lack of additional benefit with nerve root infiltration for lumbar disc herniation by the addition of steroids to lidocaine.

3.4 Evidence of Effectiveness of Local Anesthetic and Steroids

Evidence synthesis has been carried out in multiple formats for all modalities of injection therapy with local anesthetics, steroids, or combinations. The comparative evidence has been extensive for epidural injection therapy, with minimal evidence for facet joint injection therapy (30,31). The majority of the systematic reviews utilized lidocaine alone and lidocaine with steroids (12-15,17), and finally bupivacaine alone and bupivacaine with steroids (17). A systematic review (15) assessed the effectiveness of sodium chloride solution in the epidural space along with effectiveness of steroids administered alone or in combination with sodium chloride solutions. Three (15,17,18) systematic reviews utilized conventional dual-arm and single-arm meta-analysis. There was no significant difference either with pain level or disability status with sodium chloride solution alone or steroids alone, lidocaine alone or with lidocaine and

steroids and bupivacaine alone or bupivacaine with steroids.

With analysis of the effect of sodium chloride solution alone or steroids alone in the epidural space, dual arm analysis, as shown in Fig. 4, showed no significant difference with incorporation of 3 studies into the analysis at 3-month follow-up (113-115).

As shown in Fig. 5, there was improvement from baseline at 3 months in patients treated with epidural saline utilizing a single-arm analysis. As shown in Fig. 6, there was improvement with epidural steroids at 3-month follow-up also. The differences between pain relief and functional status improvement between epidurally administered sodium chloride solution alone or epidurally administered steroids, as shown in Figs. 4 to 6, were smaller than expected. The pooled mean difference of pain scores from baseline to 3-month follow-up with epidural steroids was 23.17-point decrease (Fig. 6A), whereas it was 21.84 points decrease with sodium chloride solution alone (Fig. 5A). Further, functional status improvement also showed a 12.12 decrease with steroids at 3-month follow-up as shown in Fig. 6B, whereas, it was 9.86 points as shown in Fig. 5B. Thus, this evidence shows steroids administered alone or with sodium chloride

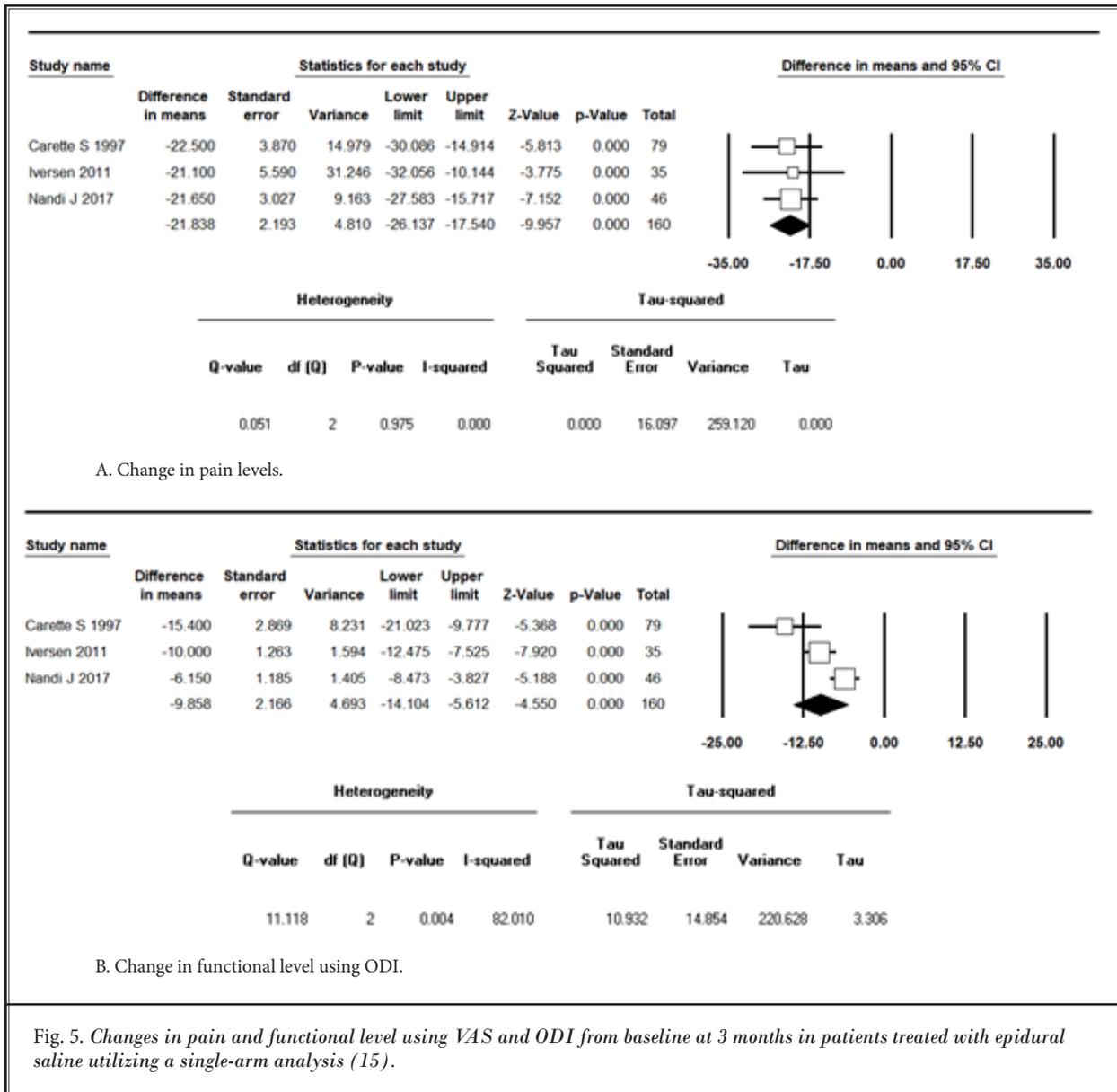


Fig. 5. Changes in pain and functional level using VAS and ODI from baseline at 3 months in patients treated with epidural saline utilizing a single-arm analysis (15).

solution is similar to sodium chloride solution alone.

Manchikanti et al (17) assessed the role of bupivacaine with or without steroids with epidural injections in 4 manuscripts (116-119), with one lumbar interlaminar epidural injection (119) and 3 lumbar transforaminal epidural injections (116-118). This systematic review was separately performed for bupivacaine alone as it was not shown to be as effective as its actions are different compared to lidocaine. Bupivacaine may

act differently and provide longer term relief based on its pharmacological activity. With appropriate methodologic quality assessment and outcome parameters a meta-analysis consisting of dual-arm meta-analysis and single-arm meta-analysis was performed. As shown in Fig. 7, while evidence appears in favor of bupivacaine with steroids, there was no significant difference between bupivacaine alone or bupivacaine with steroids, using the dual-arm meta-analysis. In contrast, with single-arm meta-analysis the pain level

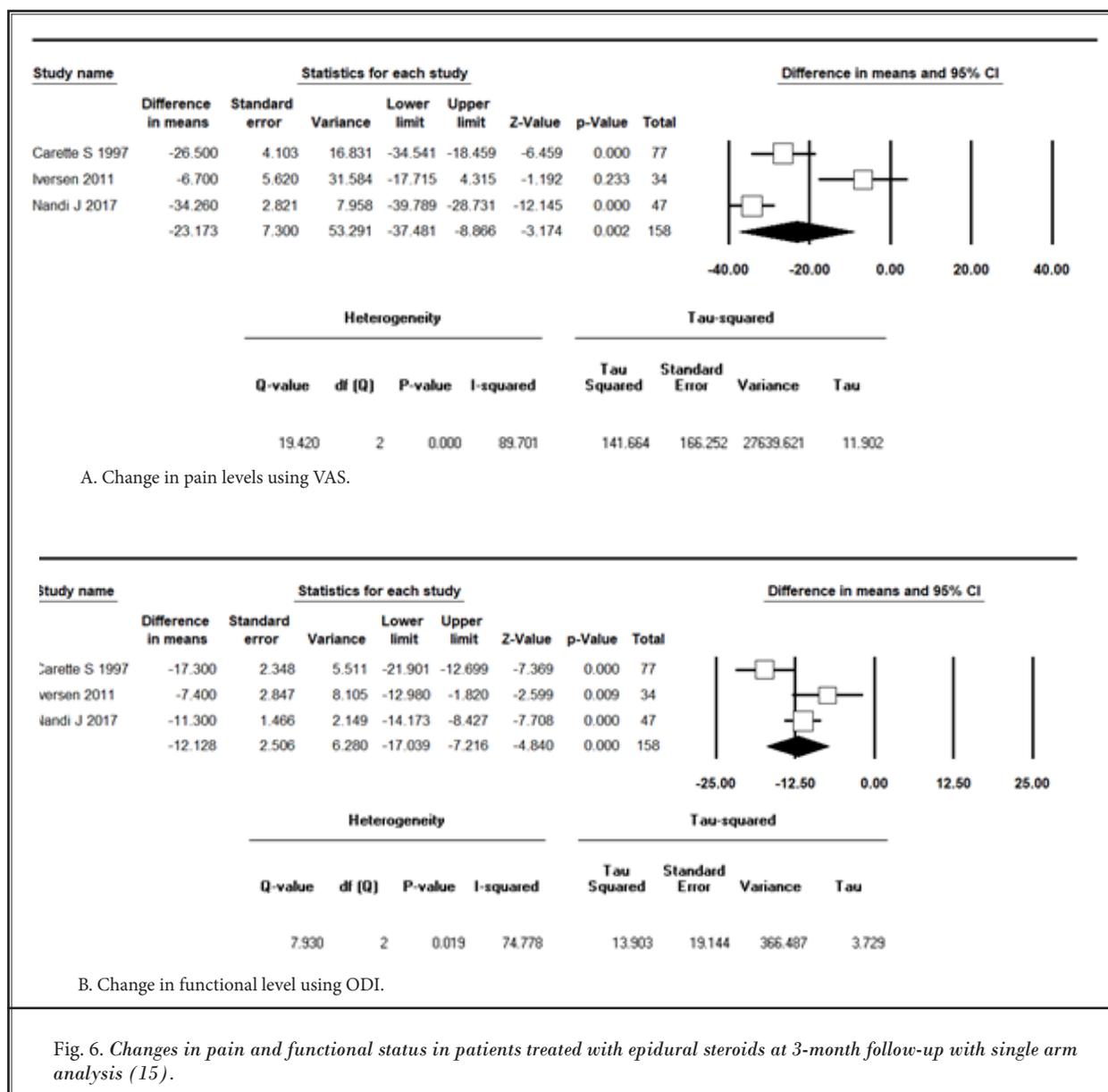
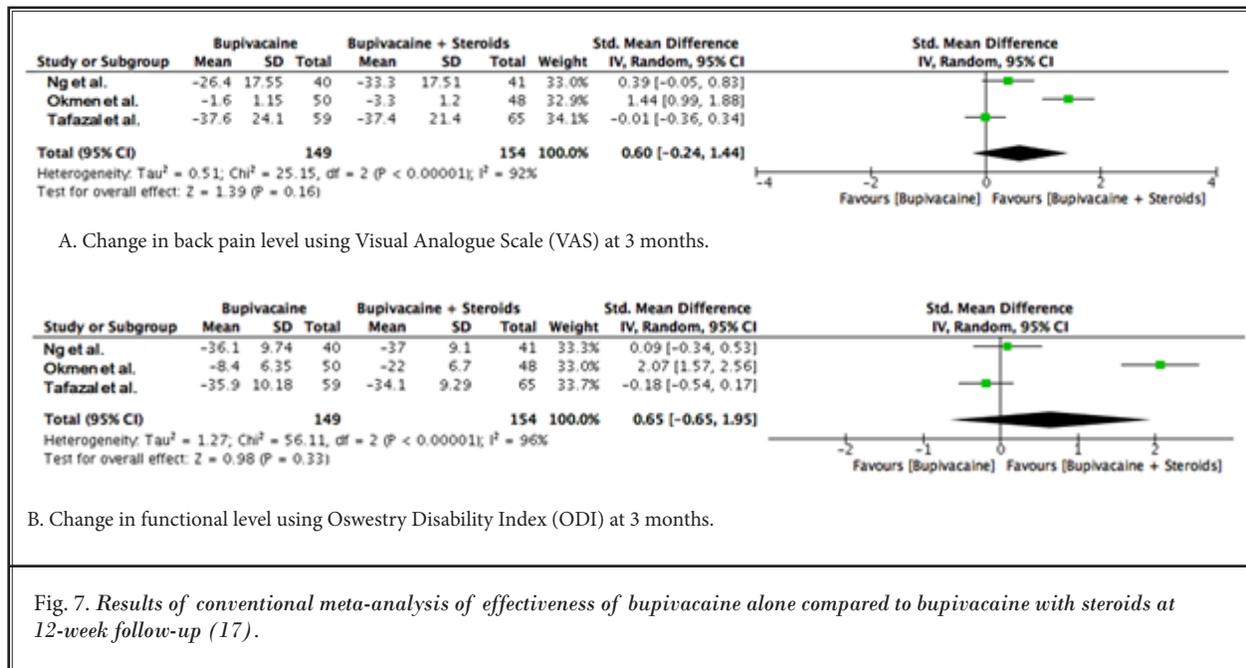


Fig. 6. Changes in pain and functional status in patients treated with epidural steroids at 3-month follow-up with single arm analysis (15).

decrease was 39.99 points from baseline to 12 weeks with bupivacaine compared to 41.93 points decrease with bupivacaine and steroids (Fig. 8). Functional level also showed similar improvement in bupivacaine alone and bupivacaine with steroid (Fig. 9).

Single-arm analysis results are shown in Fig. 8 with changes in the pain, whereas, Fig. 9 shows changes in functional level. Overall, the results are not conclusive without further studies and the ability to assess long-term follow-up.

In contrast, lidocaine has been extensively studied including those of equivalency or non-inferiority trials (12,14,15,17,18). The results show a definitive response. Knezevic et al (18) performed a systematic review utilizing 15 RCTs with all of them utilizing comparative active control design (120-134) and 13 of them comparing appropriate data outcome parameters of lidocaine alone compared to lidocaine with steroids. This analysis showed Level II or moderate evidence for short-term and long-term improvement in



pain and function with the application of epidural injections with local anesthetic with or without steroid in managing spinal pain of multiple origins. As shown in Fig. 10, with inclusion of 15 studies (120-134), utilizing a single-arm analysis local anesthetic alone or local anesthetic with steroids were shown to be effective from baseline to 12-month follow-up period with no significant difference identified. The proportion of patients responding with significant improvement of 50% pain relief and functional status improvement as shown in Table 1 was evaluated in 13 studies. Overall, patients who are judged to be responsive with first 2 procedures, showed a higher proportion responding at end of the year with a pooled response of 63% when all patients are included with all 12 studies which met inclusion criteria, whereas the significant improvement response was seen in 75% with the lidocaine only group and 78% in the lidocaine with steroid group. Single-arm analysis of lidocaine alone, or with lidocaine with steroids, showed no significant difference as shown in Fig. 11. They also analyzed the data for 24-month follow-up with no significant difference noted between local anesthetic and local anesthetic with steroids as shown in Fig. 12 with pain and function. With single-arm analysis as shown in Fig. 13, both lidocaine alone compared to lidocaine with steroids showed significant improve-

ment with no significant difference between the groups with lidocaine or lidocaine with steroids. Only 11 studies met the inclusion criteria to be included for 24-month analysis. Further, as shown in Table 2 significant improvement was also shown to be present at 24 months in 57% of the pooled data with the lidocaine only group, whereas it was 63% when all patients were considered; however, the data improved at 2 years to 68% in the lidocaine only group compared to 74% in the lidocaine and steroids group with no significant difference in any of the data. Only the studies with 2-year follow-up with all the data available were utilized excluding 2 studies.

Multiple facet joint nerve blocks were also assessed using local anesthetic alone or local anesthetic with steroids with no significant difference, either with diagnostic facet joint nerve blocks or therapeutic facet joint nerve blocks (46-48). The evidence for neural blockade with or without steroid with local anesthetic with or without steroids has not been assessed. There is no significant data evaluating the role of local anesthetic alone with joint injections, even though anecdotal experience shows that in the majority of the patients, local anesthetics alone are equally as effective, as local anesthetic with steroids. The majority of the studies have been utilizing non-steroidal solutions with hyaluronic acid, as well as platelet rich plasma

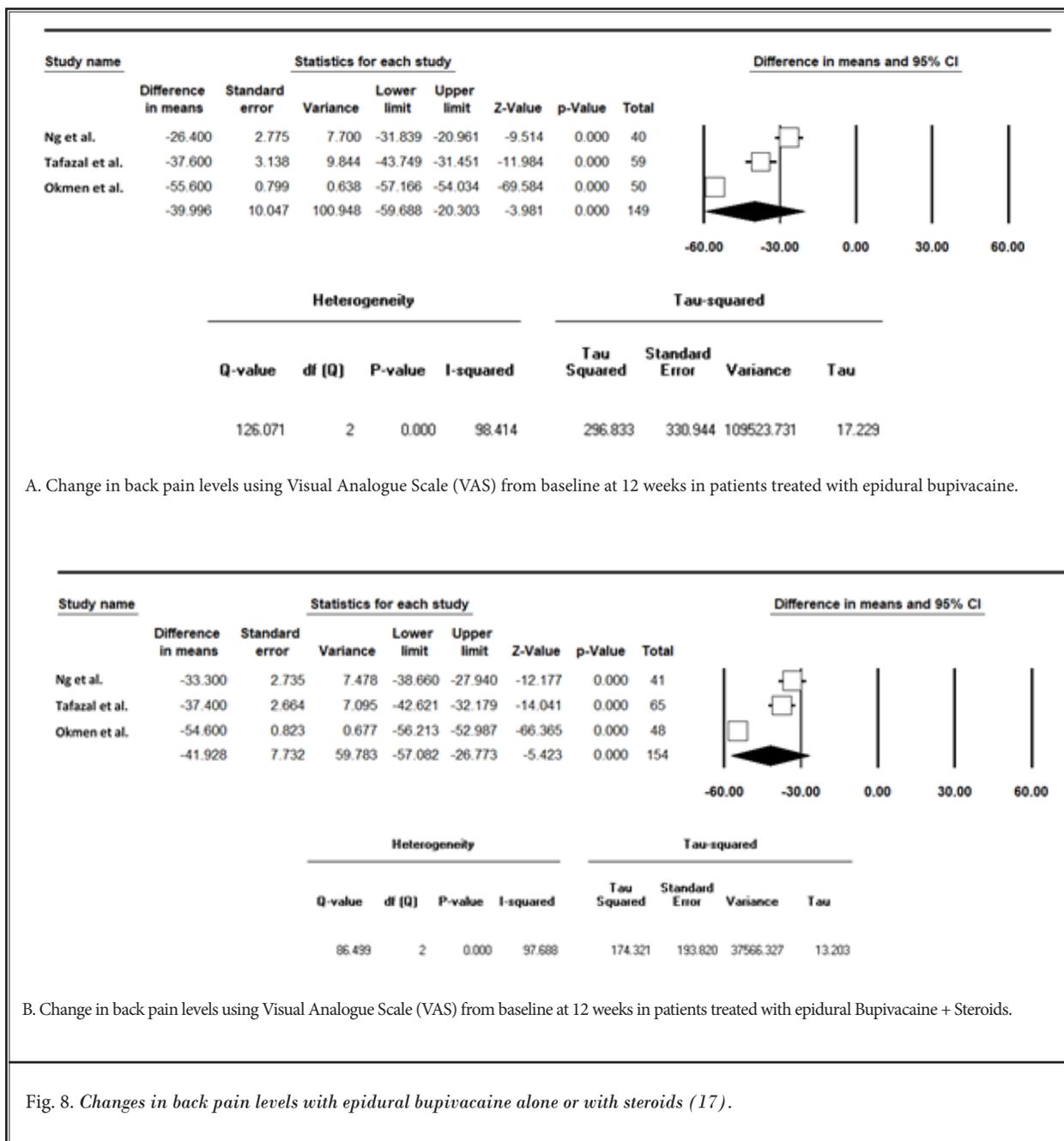
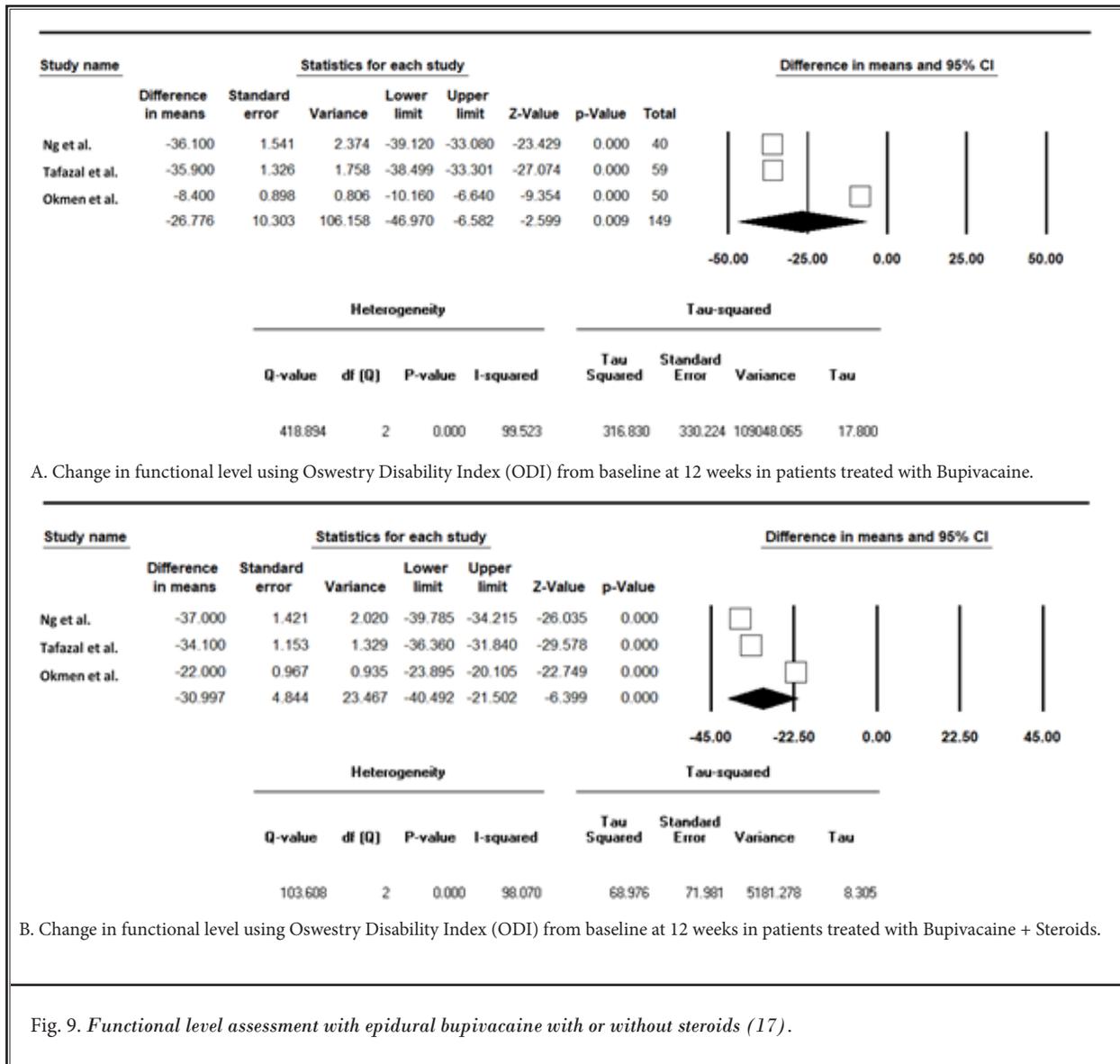


Fig. 8. Changes in back pain levels with epidural bupivacaine alone or with steroids (17).

(PRP), and stem cells (6,18-23,45,76). The principles of regenerative medicine have been extensively applied in managing spinal pain along with the development of guidelines (70,).

3.5 Side Effects of Steroids

The pharmacokinetics of corticosteroids continues to be complex. With intramuscular administration, absorption of the water-soluble sodium phosphate



and sodium succinate source is rapid, whereas the rate of absorption of lipid soluble acetate and acetonide is much slower (135-139). The subject of interest for this discussion is the role of systematic absorption of epidural steroids which has been explored in a few reports. In one of the reports, Janicki et al (138) reported pharmacokinetic analysis of methylprednisolone after epidural administration in rabbits, with only traces of methylprednisolone being detected at 6 and 12 hours after administration of the highest epidural dose of

the drug (5 mg/kg). Further, plasma methylprednisolone doses at all sampling times for the epidural doses of 2.5 and 1.25 mg/kg were also not detectable. Others have also reported being unable to detect methylprednisolone in blood samples (136). However, Friedly et al (139) in a study of the systemic effects of epidural steroid injections for spinal stenosis showed that of the 200 patients receiving corticosteroid, 32 patients or 20.3% experienced cortisol reduction at 3 weeks of $\geq 50\%$ compared with 10 patients (6.7%) treated with

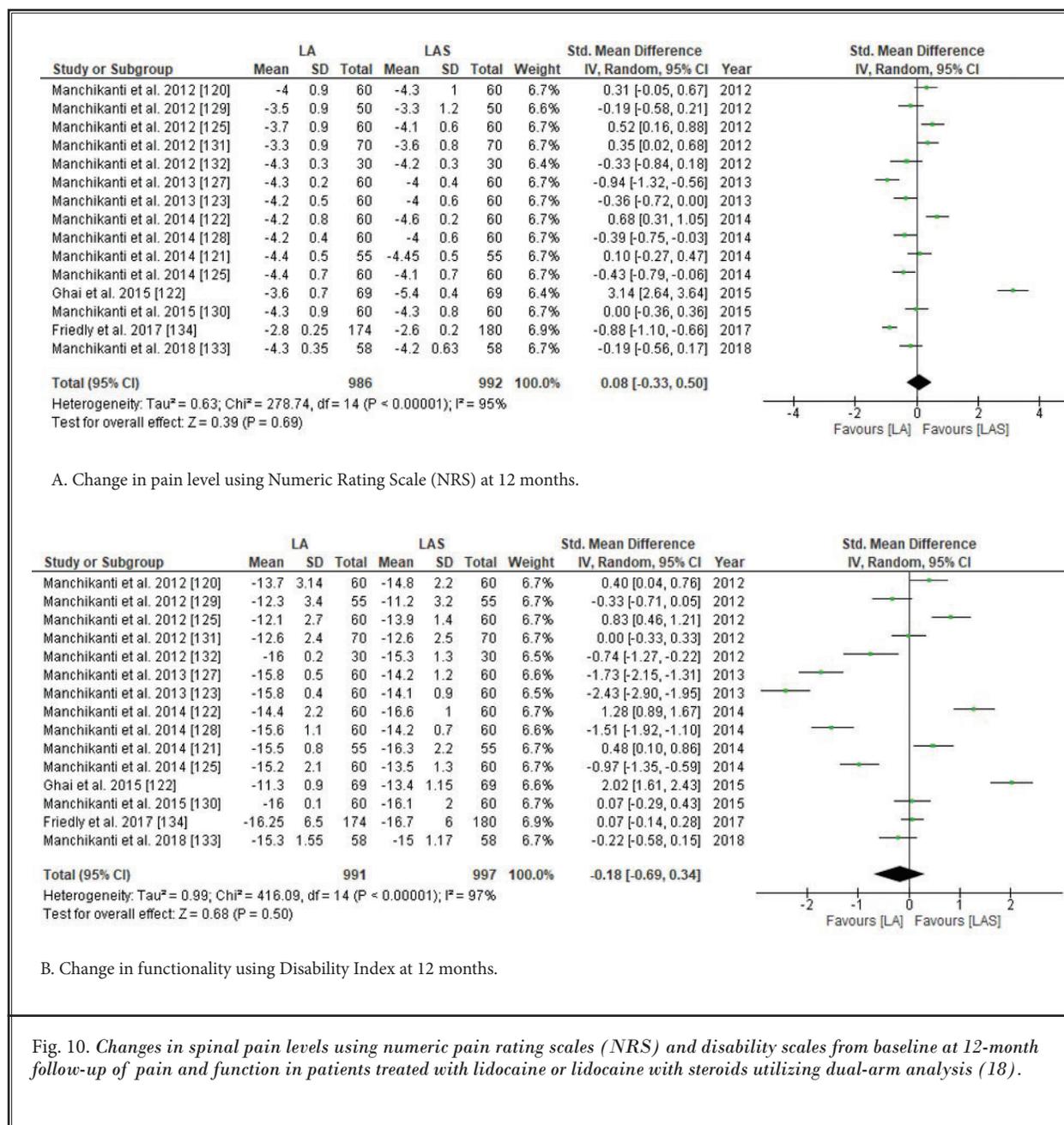


Fig. 10. Changes in spinal pain levels using numeric pain rating scales (NRS) and disability scales from baseline at 12-month follow-up of pain and function in patients treated with lidocaine or lidocaine with steroids utilizing dual-arm analysis (18).

lidocaine only. The effect on 3-week cortisol changes did not differ by patient level characteristics. They also showed that those treated with methylprednisolone or triamcinolone had an average 3-week cortisol reduction of 41% and 41.6% from baseline, respectively. Further comparison with patients treated with betamethasone

or dexamethasone, found no significant changes with cortisol and they were similar to lidocaine alone. They concluded that the higher rates of cortisol suppression at 3 weeks in those receiving epidural corticosteroid injections, particularly with longer acting insoluble corticosteroid formulations, are consistent with sus-

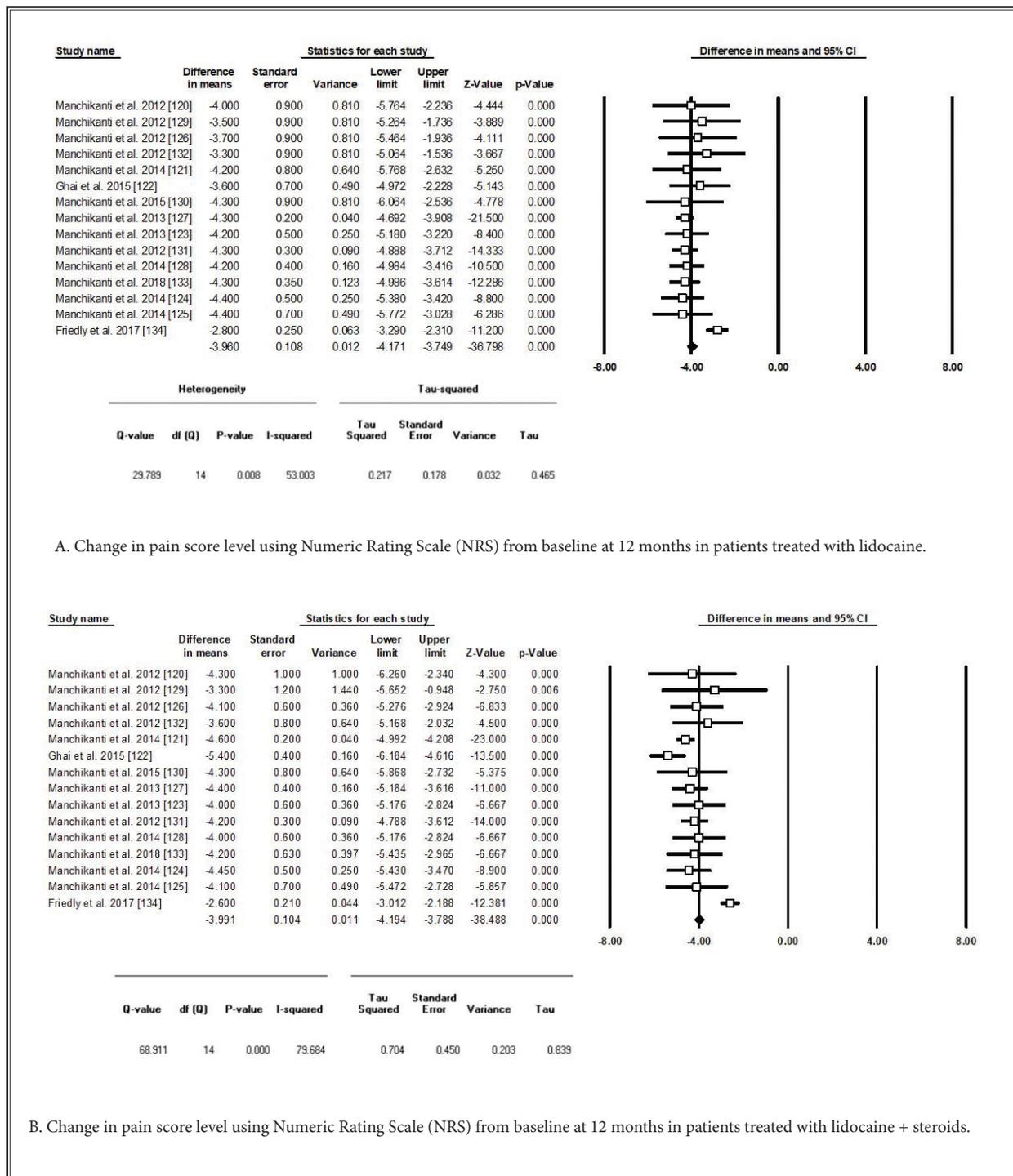
Table 1. Significant improvement at 12 months – significant improvement ($\geq 50\%$) of pain and function.

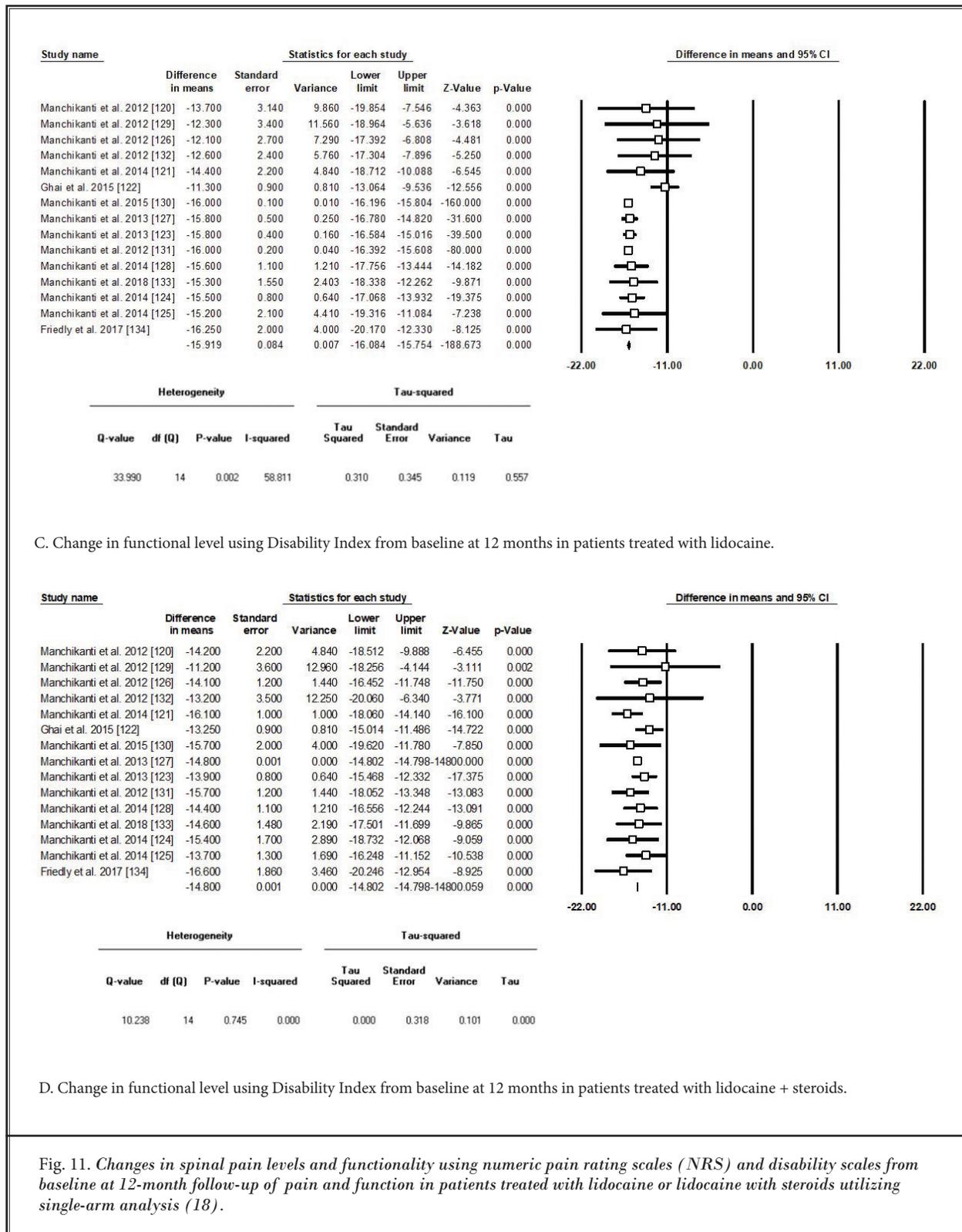
Study	All patients			Responsive Patients		
	Lidocaine Only	Lidocaine + Steroids	Difference (p value)	Lidocaine Only	Lidocaine + Steroids	Difference
Disc herniation						
Manchikanti et al (125)	67% (40/60)	72% (43/60)	0.5536	85% (40/47)	84% (42/50)	0.8924
Manchikanti et al (131)	67% (40/60)	85% (51/60)	0.0215	80% (40/50)	86% (51/59)	0.4050
Manchikanti et al (121)	72% (43/60)	68% (41/60)	0.6340	77% (41/53)	82% (41/50)	0.5324
Manchikanti et al (122)	71% (39/55)	84% (46/55)	0.1041	80% (39/49)	90% (46/51)	0.1625
Manchikanti et al (123)	75% (45/60)	57% (34/60)	0.0382	92% (45/49)	73% (33/45)	0.0150
Pooled#	70% (207/295)	73% (215/295)	0.4260	83% (205/248)	84% (213/255)	0.7628
Discogenic pain						
Manchikanti et al (124)	56% (34/60)	68% (41/60)	0.1775	84% (28/33)	85% (35/41)	0.9064
Manchikanti et al (125)	77% (46/60)	67% (40/60)	0.2244	84% (45/54)	71% (38/54)	0.1074
Manchikanti et al (126)	72% (43/60)	68% (41/60)	0.6340	78% (43/55)	73% (41/56)	0.5432
Pooled	68% (123/180)	67% (121/180)	0.8397	82% (116/142)	75% (114/151)	0.1464
Spinal stenosis						
Manchikanti et al (127)	44% (22/50)	46% (23/50)	0.5466	60% (22/37)	60% (22/37)	1.000
Manchikanti et al (128)	73% (44/60)	73% (44/60)	1.000	86% (44/51)	83% (44/53)	0.6743
Manchikanti et al (129)	73% (22/30)	70% (21/30)	0.7985	76% (22/29)	77% (20/26)	0.9311
Pooled	63% (88/140)	63% (88/140)	1.000	75% (88/117)	74% (86/116)	0.8613
Post-surgery syndrome						
Manchikanti et al (130)	53% (37/70)	59% (41/70)	0.4761	70% (37/53)	52% (42/56)	0.0555
Manchikanti et al (131)	74% (43/58)	69% (40/58)	0.5526	79% (42/53)	81% (38/47)	0.8041
Pooled	63% (80/128)	63% (81/128)	0.9340	75% (79/106)	78% (80/103)	0.6100

tained systemic absorption of corticosteroid. Hooten et al (140) showed that terminal elimination half-life of lumbar epidurally administered triamcinolone in a non-compartmental analysis was 523 hours (almost 22 days), and the peak triamcinolone concentration of 4.1 ng/mL was detected within 24 hours after administration. This elimination half-life after lumbar epidural administration is much longer than the elimination half-life of intravenous administration and is likely explained by the suspension and re-distribution of the depo preparation within the epidural fat and the epidural anatomy (141).

Risk of reductions in bone density have been reported in high dose steroids (142), though lower doses were potentially safe. Symptomatic HPA suppression

has been reported rarely to occasionally. Abdul et al (143) in 2017 reported that, after one epidural injection of 80 mg of methylprednisolone, 87% of patients exhibited hypothalamic-pituitary-adrenal axis suppression at day 7 post-injection, 43% at day 14, and 7% at day 28. Habib et al (144) in 2013, found a dose-dependent effect in a study examining the magnitude and duration of this suppression after a single epidural injection of methylprednisolone. 86% of patients who received an 80 mg dose were reported to have laboratory-confirmed hypothalamic-pituitary-adrenal axis suppression one week post-injection compared to 53% of those receiving a 40 mg dose; 20% of all participants had continued suppression at 4 weeks post-injection. Steroid solubility is a factor in endo-





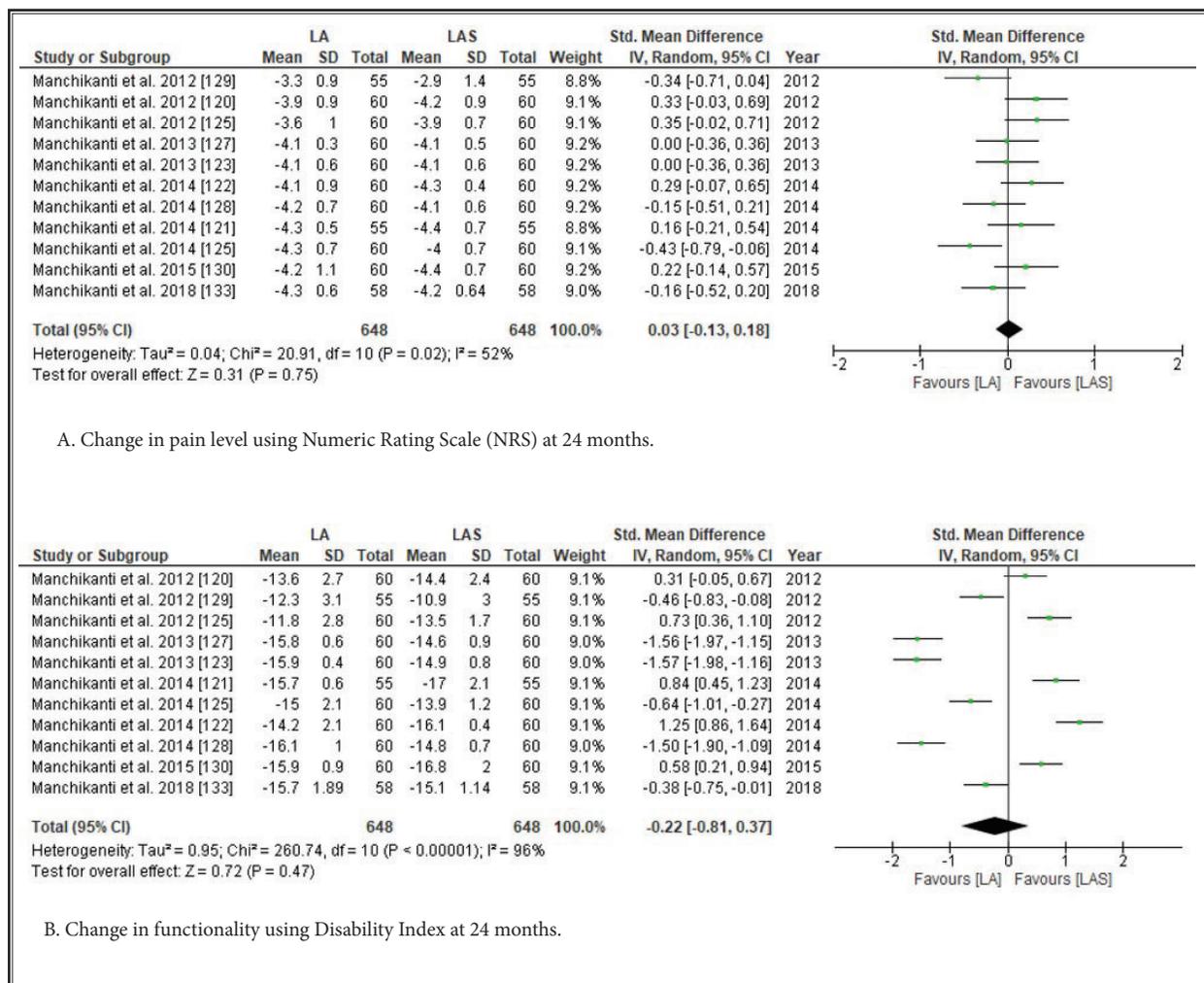
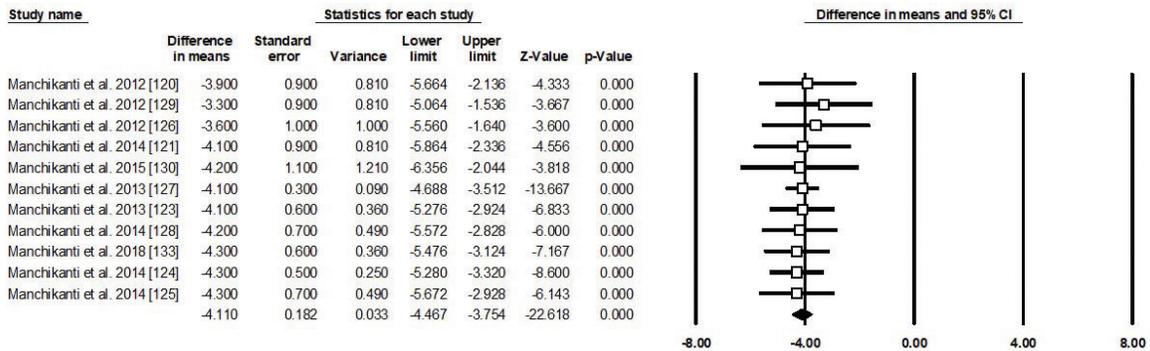
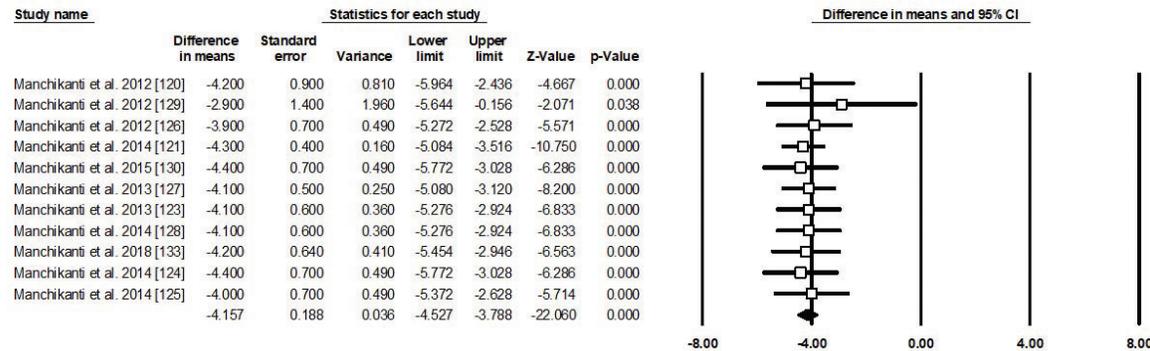


Fig. 12. Changes in spinal pain levels and functionality using Numeric Pain Rating scales (NRS) and disability scales from baseline at 24-month follow-up of pain and function in patients treated with lidocaine or lidocaine with steroids with dual-arm analysis (18).



Q-value	df (Q)	P-value	I-squared	Tau Squared	Standard Error	Variance	Tau
1.468	10	0.999	0.000	0.000	0.181	0.033	0.000

A. Change in pain score level using Numeric Rating Scale (NRS) from baseline at 24 months in patients treated with lidocaine.



Heterogeneity				Tau-squared			
Q-value	df (Q)	P-value	I-squared	Tau Squared	Standard Error	Variance	Tau
1.398	10	0.999	0.000	0.000	0.180	0.033	0.000

B. Change in pain score level using Numeric Rating Scale (NRS) from baseline at 24 months in patients treated with lidocaine + steroids.

Steroid Distancing In Interventional Pain Management

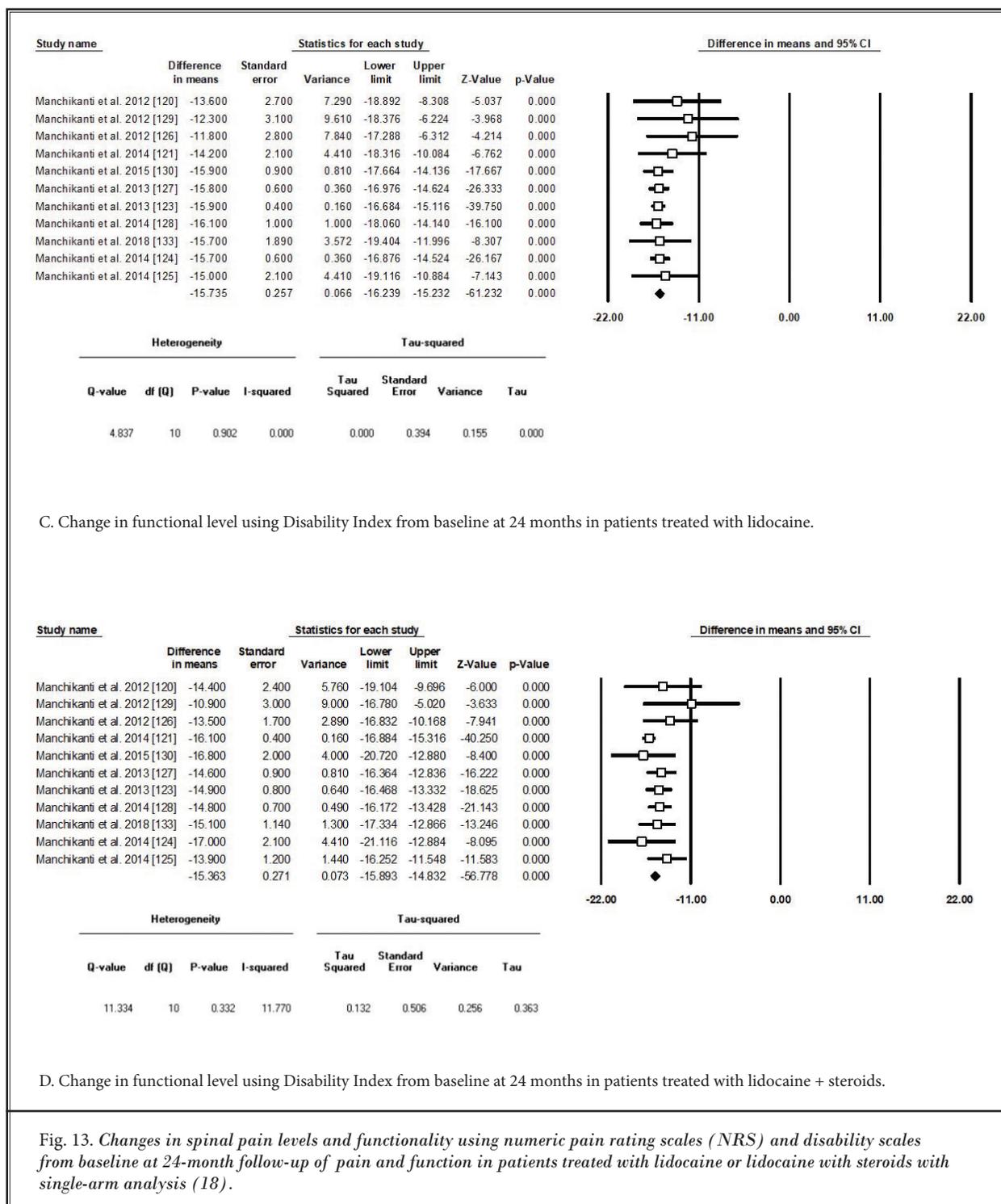


Table 2. Significant improvement at 24 months – significant improvement ($\geq 50\%$) of pain and function.

Study	All patients			Responsive Patients		
	Lidocaine Only	Lidocaine + Steroids	Difference	Lidocaine Only	Lidocaine + Steroids	Difference
Disc herniation						
Manchikanti et al (125)	60% (36/60)	65% (39/60)	0.5732	77% (36/47)	76% (38/50)	0.9081
Manchikanti et al (131)	60% (36/60)	70% (42/60)	0.2528	72% (36/50)	71% (42/59)	0.9087
Manchikanti et al (121)	72% (43/60)	68% (41/60)	0.6340	77% (41/53)	80% (40/50)	0.7126
Manchikanti et al (122)	71% (39/55)	80% (44/55)	0.2747	80% (39/49)	86% (44/51)	0.4263
Manchikanti et al (123)	65% (39/60)	57% (34/60)	0.3710	80% (39/45)	73% (33/45)	0.4361
Pooled#	65% (193/295)	68% (200/295)	0.4405	77% (191/248)	77% (197/255)	1.0000
Discogenic pain						
Manchikanti et al (124)	54% (32/60)	60% (36/60)	0.5086	84% (28/33)	73% (30/41)	0.4856
Manchikanti et al (125)	72% (43/60)	67% (40/60)	0.5536	78% (42/54)	70% (38/54)	0.3455
Manchikanti et al (126)	73% (44/60)	70% (42/60)	0.7170	78% (43/55)	75% (42/56)	0.7107
Pooled	66% (119/180)	66% (118/180)	0.9204	80% (113/142)	73% (110/151)	0.1592
Spinal stenosis						
Manchikanti et al (127)	38% (19/50)	44% (22/50)	0.5439	51% (19/37)	57% (21/37)	0.6071
Manchikanti et al (128)	72% (43/60)	73% (44/60)	0.9028	84% (43/51)	85% (45/53)	0.8885
Pooled	56% (62/110)	60% (66/110)	0.5487	70% (62/88)	73% (66/90)	0.6584
Post-surgery syndrome						
Manchikanti et al (130)	47% (33/70)	58% (39/70)	0.1941	62% (33/53)	69% (39/56)	0.4440
Manchikanti et al (131)	69% (40/58)	71% (41/58)	0.8150	74% (39/53)	79% (37/47)	0.5590
Pooled	57% (73/128)	63% (80/128)	0.3281	68% (72/106)	74% (76/103)	0.3406

crine influence; longer-acting agents (triamcinolone and methylprednisolone) have been found to suppress cortisol production for a longer duration than more soluble agents (dexamethasone and betamethasone) (139).

Corticosteroids have anti-inflammatory effects; they reduce pain related to inflammation by down-regulation of the immune function as well as reduction of inflammatory cells and mediators (lymphocytes, macrophages, and mast cells) (145,146). Although it has not been directly studied, the endocrine disruption from a single epidural steroid injection suggests similar systemic effects on immune response. The use of systemic corticosteroids can adversely affect the innate (immediate) immune response by impairing the ability of neutrophils to migrate to infection sites

as well as macrophage and monocyte function. The adaptive immune response (leads to immunological memory) is also negatively affected by corticosteroids, as the capability of plasma cells to produce immunoglobulins IgG and IgA is reduced by 10-20% after exposure. Injection therapy plausibly has similar effects to the oral administration effects described in the literature (147).

Consequently, adverse immune influences of corticosteroids during influenza infection is of increased concern for those prescribed or injected with corticosteroids, with specific concern during the current COVID-19 pandemic. Meta-analysis of orally-administered corticosteroid versus placebo demonstrates an increased risk of influenza infection within the steroid group. One study found a dose-dependent

relationship for infection risk, showing a relative risk of 1.5 with low doses of steroids and a relative risk greater than 8 with doses above 40 mg/day (148). In another study, rheumatoid arthritis patients taking oral prednisone had relative risks ranging from 1.4 (< 5 mg/day dose) to 2.3 (> 10 mg/day dose) for hospitalization due to pneumonia compared to rheumatoid arthritis patients not taking oral prednisone (149). Although data for single-dose exposure to corticosteroids is limited, early evidence is provided in a report on an observational cohort from the Mayo Clinic. Over five influenza seasons, an increased incidence of influenza infection was associated with steroid injection compared to no injection (150). There are currently no studies specifically examining the relationship between corticosteroid injections and COVID-19, however, the findings presented here raise concern for a potential relationship.

Thus, the literature surrounding infrequent adverse effects of epidural corticosteroids continues to accumulate (151-153), with alterations in blood glucose levels among patients with diabetes (154,155), and prolonged effects on the hypothalamic-pituitary-adrenal (HPA) axis (156). Further, it has also been reported that systemic side effects are common with long-term administration of steroids (157,158). Lamer et al (151) in a study of 8 patients also assessed serum triamcinolone levels following cervical interlaminar epidural injection. Data of the pharmacokinetics showed peak triamcinolone concentration (C max) of 5.4 ng/mL median value within 22.1 hours (T max) of administration. The terminal elimination half-life was 219 hours, the median value. They also compared the results of this study with the previous study of lumbar interlaminar epidural injections (140) and showed similar patterns. This comparison also showed that while the pharmacokinetic profile is similar, the T max is earlier and T ½ is shorter for the cervical compared to the lumbar epidural steroid injection. In similar lines with other investigators, recently, Sim et al (59) assessed the relationship between epidural steroid dose and separation of HPA access. In the analysis of 30 patients with administration of triamcinolone, either 40 mg or 20 mg, they showed that triamcinolone group showed longer HPA separation, 19.7 ± 3.1 days compared to triamcinolone 20 mg group (8.0 ± 2.4 days) and the recovery rate of triamcinolone 40 mg group was lower than that of 20 mg group with a significant difference (P value > 0.015) as shown in Fig. 14.

In another manuscript, Chon and Moon (60)

reported that in all subjects who received epidural steroid injections with triamcinolone acetate, 40 mg were suppressed temporarily and was restored after a mean of 19.9 ± 6.8 days.

The data also shows that intravenous triamcinolone acetonide pharmacokinetics using the soluble form have been previously determined, demonstrating a half-life of approximately 1.5 to 2 hours (159,160). However, in contrast to intravenous administration, intraarticular knee injection of a suspension of acetonide showed vastly different results wherein triamcinolone acetonide was detected in serum for more than 2 weeks and the half-life ranged from 77 to 446 hours (161). Thus, it is crucial to understand the different mechanisms of short-acting and long-acting drugs, along with particulate sizes. It is also hypothesized that there is less sequestration of particulate steroids in the cervical epidural space, consequently with faster absorption. Table 3 shows the profile of commonly used epidural steroids based on the data derived from multiple sources (64,135-137,157,162,163). Table 4 shows formulations of commonly used epidural steroids. Dexamethasone is not being discussed since it is a non-particulate and short-acting steroid with the least side effects, but it is associated with some side effects.

Overall, systemic side effects are significant with the influence of corticosteroids on metabolism of carbohydrates, fats, proteins, and purine. They can also affect electrolyte and water balance and may affect the functions of the central nervous system (CNS) and of the cardiovascular, renal, endocrine, reproductive, and immune systems, as well as the bones and muscles (158). Long-term effects may be caused directly by excess glucocorticoid in the circulation or indirectly through suppression of the HPA. It is also common that patients presenting to interventional pain management may be taking long-term steroids for multiple medical problems and also may be receiving intraarticular steroid injections.

The specific effects on the immune system are worrisome during the COVID-19 pandemic. While there are no data available in regards to the effects of epidural administration of glucocorticoids on the immune system, there are data available regarding systemic administration with high dose glucocorticoid therapy, equivalent to doses of 40 mg or more of prednisone per day. With high doses, there is an immediate risk of infection due to inhibition of phagocyte cell function, which abates after completion of therapy

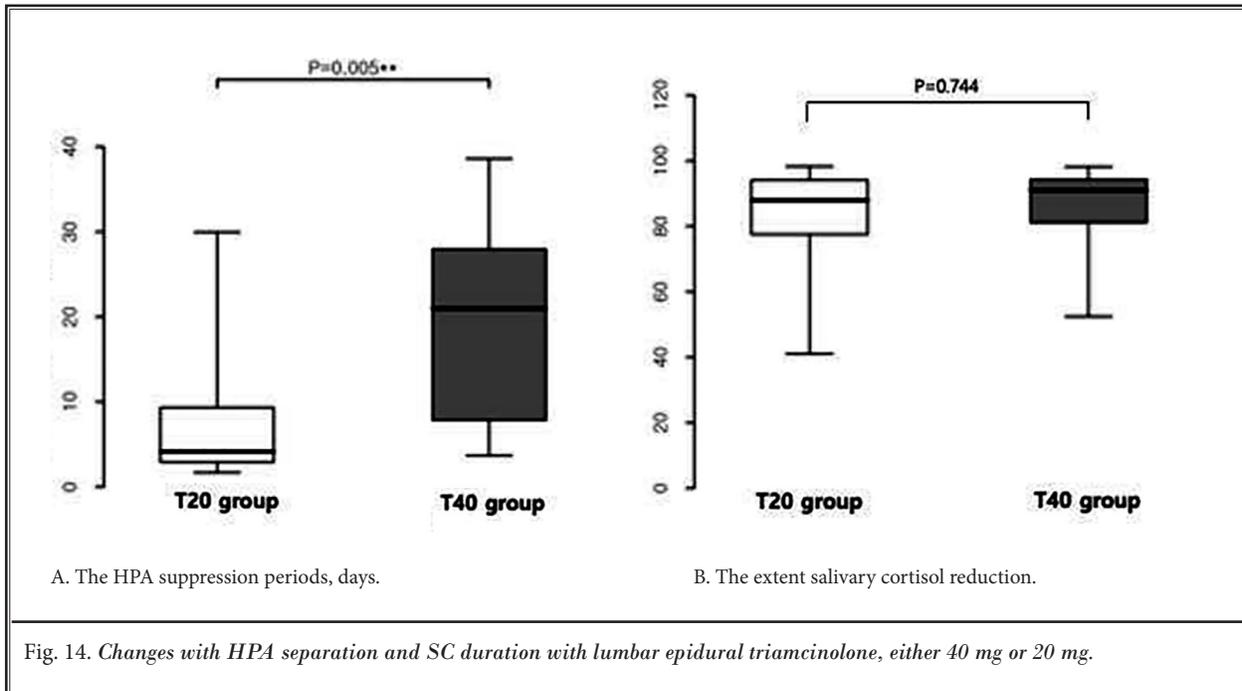


Fig. 14. Changes with HPA separation and SC duration with lumbar epidural triamcinolone, either 40 mg or 20 mg.

Table 3. Profile of commonly used epidural steroids.

Drug	Equivalent Dose	Epidural Dose	Anti-inflammatory Potency	Sodium Retention Capacity	Duration of Adrenal Suppression		
					IM	Single Epidural	Three Epidurals
Hydrocortisone	20 mg	NA	1	1	NA	NA	NA
Depomethylprednisolone (Depo-Medrol)	4 mg	40-80 mg	5	0.5	1-6 weeks	1-3 weeks	NA
Triamcinolone acetonide (Kenalog)	4 mg	40-80 mg	5	0	2-6 weeks	3-5 weeks	2-3 months
Betamethasone (Celestone Soluspan)	0.6 mg	6-12 mg	25	0	1-2 weeks	NA	NA

NA=not applicable

Data adapted and modified from McEvoy et al (135), Jacobs et al (136), Kay et al (137), Hsu et al (157), Mikhail et al (162,163), and Schimmer and Parker (64).

(65). In patients with rheumatoid arthritis, acute effects of 1 gm of intravenous methylprednisolone showed development of leukopenia within 2 hours of the dose, which peaked at 6 hours, and resolved by 24 hours. In addition, doses of less than 40 mg, considered as low to moderate, have been shown to reduce T lymphocytes with delayed hypersensitivity responses. With long-term low dose usage, some inhibition of immune responses may increase with duration of therapy (66). Multiple issues related to vaccination have

been discussed in the past (67-69); however, not with COVID-19 virus. Considering the literature, short-term therapy with low dose within appropriate duration of 6 to 13 weeks may not have any significant effect. The Advisory Committee on Immunization Practices (ACIP) (62) and the Centers for Disease Control and Prevention (CDC) (63) to defer live vaccination at least one month after discontinuation of high dose systemically absorbed glucocorticoid therapy administered for 14 days.

Table 4. Formulations of commonly used epidural steroids.

Amount of steroid	Depo-Medrol Methylprednisolone			Aristocort Triamcinolone Diacetate	Kenalog Triamcinolone Acetonide	Celestone Betamethasone
	20 mg/mL	40 mg/mL	80 mg/mL	40 mg/mL	40 mg/mL	6 mg/ mL
Polyethylene glycol 3350	29.5	29.1	28.2	30	--	--
Polysorbate 80	1.97	1.94	1.88	2	0.4	--
Monobasic sodium phosphate	6.9	6.8	6.59	--	--	3.4
Benzyl alcohol	9.3	9.16	8.8	9	9	--
Dibasic sodium phosphate	--	--	--	--	--	7.1
Edetate disodium	--	--	--	--	--	0.1
Benzalkonium chloride	--	--	--	--	--	0.2

3.6 Side Effects of Local Anesthetics

Historically, the use of procaine was extensively utilized following cocaine; however, the introduction of lidocaine in 1948 and bupivacaine, which was introduced in 1963, has been extensively used outside of the epidural space with lidocaine also used for intraarticular injections in chronic pain management. The mechanism of action of intravenous lidocaine in neuropathic pain cannot be explained by blockade of voltage-gated Na⁺ channels alone. The clinical effects include reduction of spontaneous pain, allodynia, and hyperalgesia. Further, local anesthetic infusions have been utilized in various types of pain providing longer term relief than the expected duration of the local anesthetic (164). Local anesthetics also have systemic and local toxic effects. Systemic toxicity relates to the relatively narrow difference between therapeutic plasma levels and toxic levels (165). Peak plasma levels are determined by the dose and rate of systemic absorption. The genes controlling the subunit of Na⁺ channels give rise to different pharmacological and biophysiological profiles of Na⁺ channels through the body (164). Overall, levobupivacaine has lower systemic toxicity than other amides because of its lower affinity for cardiac channels (166). Intraarticular local anesthetics may cause chondrotoxicity; however, chondrotoxicity is worse with bupivacaine or mepivacaine. While Methemoglobinemia is a major issue with prilocaine, benzocaine and lidocaine can also cause methemoglobinemia (167,168).

Local anesthetic toxicity affects 2 organs that inherently are less tolerant of anaerobic metabolism, the heart and brain. Cardiac toxicity is mostly

related to accidental intravascular injection, leading to the conduction disturbances, contractile dysfunction, and ventricular arrhythmias that are seen in local anesthetic induced cardiac toxicity (169). More importantly, for interventional pain physicians, the incidence of cardiac toxicity increases with bupivacaine, a longer acting anesthetic. Bupivacaine blocks inactive sodium channels during the cardiac potential at a concentration of 0.2 mcg. Bupivacaine binding is described as "fast-in, slow-out" fashion as it binds very quickly to large portion of sodium channels during the cardiac action potential, but releases from the channel slowly during diastole, resulting in a large proportion of medication accumulating at 60 to 150 beats per minute. Local anesthetic toxicity may become a serious issue, even though adverse effects are rare. From minor symptoms to major cardiac or CNS effects, local anesthetic system toxicity is an important consequence in interventional pain management. The epidemiology of local anesthetic toxicity has been reported from zero events to 25 per 10,000 nerve blocks. One study reported seizures of 79 of 10,000 brachial plexus block procedures (170,171).

Lidocaine at 5 to 10 mcg/mL will also result in substantial sodium channel blockade during a cardiac action potential. However, in contrast to bupivacaine, lidocaine follows the "fast-in, fast-out" principle, meaning it releases from sodium channels rapidly during diastole. This allows for a quick recovery, and reduced incidence of cardiac toxicity even compared to bupivacaine. Consequently, during a cardiac arrest, it may be crucial to continue resuscitation measures

until bupivacaine is completely released. CNS changes include agitation, confusion, dizziness, drowsiness, dysphoria, auditory changes, tinnitus, perioral numbness, metallic taste, and dysarthria. Without adequate recognition and treatment, these signs as symptoms can progress to seizures, respiratory arrest, and/or coma.

Historically, local anesthetic literature suggests that cardiac toxicity often presented after antecedent CNS toxicity (169). However, with more potent local anesthetics, cardiac toxicity may precede CNS toxicity. Lidocaine was utilized far more frequently than bupivacaine. Subarachnoid blockade with bupivacaine may turn out to be a disaster, specifically in cervical spine. Consequently, injections of bupivacaine in cervical or thoracic spine is contraindicated. Even then, lidocaine is also injected in extremely low concentrations of 0.5%. In the cervical spine, one must still be careful with appropriate visualization of the epidural space without any subdural or subarachnoid filling. Failure to follow basic principles can result in respiratory arrest, as well as cardiac arrest.

Apart from COVID-19 issues, steroids continue to present with multiple problems including vascular embolism related to particulate steroids with transforaminal epidural injections. These are most commonly seen with particulate steroids with triamcinolone or depomethylprednisolone. In contrast, betamethasone, which is also considered as a particulate steroid, shows less prevalence of the side effects and lesser suppression of glucocorticoid synthesis, leading to fewer complications.

4.0 DISCUSSION

The present focused narrative review shows evidence for safe and effective use of lidocaine in epidural injections and potentially bupivacaine with lack of evidence with intraarticular injections of spinal and peripheral joints. Thus, steroid distancing may be managed with regard to appropriate consideration of each patient, with lidocaine with steroids being reserved for patients with significant radiculitis and also failure to respond to lidocaine alone. This is demonstrated with multiple randomized controlled trials and also systematic reviews. Of all the systematic reviews, the most significant is the systematic review by Knezevic et al (18) with inclusion of 15 randomized controlled trials utilizing dual-arm and single-arm analysis. Multiple other systematic reviews also showed similar findings of Knezevic et al (13-15,17,18) Bupivacaine

alone showed equivocal results with equal effectiveness even though bupivacaine with steroids appear somewhat superior (17). Finally, in this review we also illustrated that sodium chloride solution in itself has similar effects as steroid, however, much less than bupivacaine alone or bupivacaine with steroids and finally lidocaine alone or lidocaine with steroids. There was no significant evidence available for intraarticular injections of the spine or extremities. Consequently, there is significant evidence from other reviews and precedents to recommend the use of local anesthetic alone in epidural injections.

Side effects are also of paramount importance. There have been numerous reports of side effects with steroids; however, utilizing lower dosages may avert this problem, specifically with duration of side effects. The literature is replete with case studies and retrospective reports; however, there is no evidence derived from randomized controlled trials. Side effects may be more significant with peripheral joint injections, not only with increased blood glucose levels and immunosuppression, etc, not only with systemic side effects, but, related to local side effects with damage to the joint tissues.

Multiple limitations include lack of evidence with multiple modes of treatment with steroids, except for epidural injections with lidocaine alone compared to lidocaine with steroids. While steroid distancing may be a temporary measure, it is crucial that the interventional pain management community study the effectiveness of various solutions including those of biologics (70).

5.0 CONCLUSION

This present manuscript about steroid distancing in interventional pain management practices during COVID-19 and beyond describes an understanding of interventional pain management literature with local anesthetics alone or with steroids. The results show lack of significant difference between local anesthetic alone compared to local anesthetic with steroids. There may be a few instances where steroids are required. With nerve blocks, it appears that there is no significant improvement with the addition of steroids. Consequently, these can be omitted. With intraarticular steroids, there are no studies using local anesthetic alone; however, this is something that needs to be looked at and most likely, local anesthetics alone will provide significant improvement in these patients.

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Author Contributions

This review manuscript was conceptualized and designed by LM and AS.

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Appendix 1

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