



RESEARCH ARTICLE

REVISED Effect of supraneural transforaminal epidural steroid injection combined with caudal epidural steroid injection with catheter in chronic radicular pain management: Double blinded randomized controlled trial. [version 2; peer review: 4 approved]

Sithapan Munjupong ¹, Wipoo Kumnerddee²

¹Department of Anaesthesiology, Phramongkutklo Hospital and College of Medicine, Bangkok, Bangkok, 10400, Thailand

²Department of Rehabilitation Medicine, Phramongkutklo Hospital and College of Medicine, Bangkok, Bangkok, 10400, Thailand

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Abstract

Background: Epidural steroid injection (ESI) has been used in managing chronic radicular pain. Regarding various techniques of ESI, the synergistic effect of caudal ESI (CESI) on transforaminal ESI (TFESI) in chronic lumbosacral radicular pain in prospective randomized controlled trial has not been determined. **Methods:** A total of 54 eligible patients with lumbosacral radicular pain were randomly allocated to undergo TFESI plus CESI (TC group) or TFESI alone (T group). The effective response to treatment was predefined by at least a 30% reduced verbal numerical rating scale (VNRS) from baseline between group comparison and the functional outcomes as measured by improved Oswestry Disability Index by least 15 points from baseline. All participants were evaluated using a single blinded outcome assessor before the procedure and at 1, 3 and 6 months after the procedure. $P < 0.05$ was considered as statistically significant.

Results: Average VNRS reduced significantly from baseline after receiving procedure at 1, 3 and 6 months in both groups (P -value < 0.05). The TC group exhibited more effective and showed significant pain relief compared with the T group at 3 months ($P = 0.01$). However, no statistical difference was observed between sub group analysis in pain relief and insignificant difference between group comparisons of functional outcomes.

Conclusions: A treatment combining TFESI and CESI showed significant pain relief over TFESI alone at 3 months. No effect was found concerning functional evaluation.

Registration: Thai Clinical Trials Registry
 ID TCTR20171101002 01/11/2017F

Open Peer Review

Reviewer Status

	Invited Reviewers			
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version 2 (revision) 24 Jul 2020	 report	 report	 report	
version 1 22 Jun 2020	 report	 report	 report	 report

1. **Steven Cohen**, Johns Hopkins school of medicine, Baltimore, USA
2. **Koravee Pasutharnchat** , Mahidol University, Bangkok, Thailand
3. **Jatuporn Eiamcharoenwit** , Prasat Neurological Institute, Bangkok, Thailand
4. **Abdul Hadi Mohamed** , International Islamic University Malaysia, Kuantan, Malaysia

Any reports and responses or comments on the

Keywords

Transforaminal, caudal, epidural steroid injections, lumbosacral radicular pain, randomized controlled trial.

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article can be found at the end of the article.

Corresponding author: Sithapan Munjupong (sithapan@gmail.com)

Author roles: **Munjupong S:** Conceptualization, Data Curation, Formal Analysis, Funding Acquisition, Investigation, Methodology, Project Administration, Resources, Supervision, Validation, Visualization, Writing – Original Draft Preparation, Writing – Review & Editing; **Kumnerddee W:** Conceptualization

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REVISED Amendments from Version 1

The 1st version was revised because there demonstrated one categorical outcome being > 50% pain relief from previous study but Bicket MC *et al.* (Pain Pract 2017;17(8):1058-65) showed the impact guidelines state that 30% or more pain relief is clinically meaningful as Dr. Cohen SP's recommendation. Therefore, we considered showing the proportion of people who also obtained > 30% pain relief in version 2 and found more effective and showed significant pain relief in combined group(TC group) at 3 months follow ups but insignificant in subgroup allocation. Moreover, 2nd version showed two fluoroscopic imaging that showing the flow of contrast which determine of deposition of steroid as Dr. Mohamed AH's suggestion. Furthermore, more detail in [Figure 3](#) showed that two participants who were excluded due to wrong allocation from progressive weakness and scheduled for surgery and alternated figure legends in [Figure 2](#) and [3](#) (version 1) were edited and showed in [Figure 4](#) and [Figure 5](#) (version 2) as peer review's guidance for good quality of the research.

Any further responses from the reviewers can be found at the end of the article

Introduction

Chronic lumbosacral radicular pain (CLRP) is a common condition in pain and spine centers. Treatment is challenging among patients who do not respond to either medication or physiotherapy and epidural steroid injection (ESI) is one commonly used intervention to alleviate radicular symptoms¹. These inhibit the synthesis of prostaglandins, interrupting nociceptive c fibers and reducing edema surrounding the nerve root²⁻⁴.

Different approaches of ESI are available, namely, transforaminal ESI (TFESI), interlaminar ESI (ILESI), and caudal ESI (CESI)⁵⁻⁹. The effectiveness of these three injected approaches has been shown. Related studies¹⁰⁻¹² have reported that TFESI was more beneficial than CESI regarding pain relief in herniated disc or radicular pain¹³. However, one recent systematic review and meta-analysis revealed TFESI could be weakly recommended over CESI¹⁴. Furthermore, one retrospective study showed adjunctive CESI on TFESI significant relieved more pain than only TFESI¹⁵. Unfortunately, a prospective study has not been conducted of the additional effects of combining the epidural steroid approach. Consequently, this study aimed to compare the effectiveness of pain relief and functional outcome between additional CESI to TFESI and TFESI separately in chronic lumbosacral radicular pain in a prospective randomized study and also to investigate possible complications during injection.

Methods

Ethical issues

The study comprised a prospective, single center, randomized, double blind, active-controlled parallel group. Permission to conduct this study was granted by the Institutional Review Board of the Royal Thai Army Medical Ethics Committee and registered with the Thai Clinical Trials Registry on 11 November 2017 ([TCTR20171101002](#)).

Participants

This study was conducted from November 2017 to January 2019. In total, 54 patients who met inclusion criteria were

recruited. Patients attending the PMK Pain Treatment Center, Phramongkutklo Hospital were informed by a nurse anesthetist about the study. Patients who indicated an interest then provided written informed consent. The inclusion criteria comprised patients aged 18 to 80 years old with a history of chronic lumbosacral radicular pain (longer than six months) having a diagnosis of either symptomatology or physical examination correlated using magnetic resonance imaging (MRI) and unsatisfactory pain control with either medication or physiotherapy. The exclusion criteria comprised patients presenting significant neurological deficit or cauda equina syndrome, no absolute contraindications to intervention from MRI such as discitis or spinal infection, coagulopathy, psychiatric problem, pregnancy, language barrier or history of allergy to local anesthetics, triamcinolone and contrast media.

Randomization and blinding

All patients were interviewed and physically examined by only one pain physician. Pain characteristics were documented and randomly allocated in two groups equally using a randomization with block size of four from a computer-generated table and concealed envelope. The random numbers were kept sealed and opened by a nurse anesthetist uninvolved in this study. Those in the TC group received CESI in addition to TFESI, and the T group received only TFESI. All participants and one nurse anesthetist, trained as outcome assessor were blinded to the study group.

Interventions

The intervention was performed as a day surgery using local anesthesia. The treatment level determined for supraneural transforaminal approach was based on clinical symptoms correlating with MRI. All patients were placed in the prone position, then pulse oximetry and noninvasive blood pressure were monitored. The lower back and buttocks areas were cleaned using sterile fashion technique.

A C-arm fluoroscope (9900 Elite, Super C, OEC, UT, USA) was adjusted and rotated obliquely 20 to 25 ° ipsilateral to the affected side and 0 to 10 ° cephalo-caudad tilt until aligned with the superior vertebral end plate. The needle entry points were identified and the skin was infiltrated with 4 to 6 mL 1% lidocaine. A Quinke needle (22-G, 10 cm long) (Unilever, Japan) was inserted in the direction of the radiation beam. The supraneural transforaminal technique was performed, and the tip of the needle was placed below the pedicle and within the upper half of the intervertebral foramen in the lateral image. Then 0.5 to 1 ml of nonionic contrast media (Omnipaque 300, GE Healthcare, Shanghai, China) was injected via extension tubing to confirm the needle's location at the target area under real time fluoroscopy. The caudal epidural space was identified using fluoroscopic guidance in the lateral position and then a 16-gauge introducer Touhy needle (Epimed International RK, Epimed International, Johnstown, NY, USA) was inserted through the sacral hiatus into the caudal space and an epidural catheter was inserted using Touhy needle. Then 0.5 to 1 ml of nonionic contrast media was injected via epidural catheter (Epimed International RK, Epimed International, Johnstown, NY, USA) under real time imaging to confirm the desirable vertebral level and covered

target site on both groups as shown in [Figure 1](#) and [Figure 2](#). T-group underwent 0.08% Levobupivacaine (Abbvie S.r.l., Italy) plus 40 mg of triamcinolone (L.B.S. Laboratory Ltd., Bangkok, Thailand) in a total volume of 3 ml via only the intervertebral foramen. Those in the TC group underwent 3 ml of 0.08% Levobupivacaine plus 40 mg of triamcinolone using the transforaminal approach combined with 10 ml of 0.025% Levobupivacaine plus 40 mg of triamcinolone via caudal epidural catheter.

Outcome measurement

The primary outcome was an effective response to treatment, predefined by at least a 30% reduced verbal numerical rating scale (VNRS; 0-100) from baseline¹⁶ between group comparisons. The secondary result was functional outcome, measured by improved Oswestry Disability Index (ODI, Thai version 1)¹⁷ at least 15 points from baseline. All participants were completely supervised and evaluated by blinded outcome assessor before the procedure, and then subsequently at 1, 3 and 6 months after procedure when attending the outpatient department of PMK Pain Treatment Center.

Sample size calculation and statistical analysis

The sample size was calculated based on the related study of Ploumis A *et al.*¹². The probability of significantly reduced pain from TFESI was 0.90, whereas the probability of signifi-

cantly reduced pain from CESI was 0.545. The result indicated 24 patients were required for each group to reach a significance level of 0.05, the power of study was set at 80%, and we added 10% more for loss to follow-up. The final number of participants totaled 27 per group. All analyses and summaries were performed with *Stata*, Version 13/SE (StataCorp, 2013, College Station, TX, USA). A *P* value <0.05 was considered statistically significant. Descriptive statistics for continuous variables were presented as mean and standard deviation (SD) for sufficiently normally distributed variables. For nominal data, absolute and relative frequencies were displayed for each category. Independent t-test and Chi-square test were performed to compare the differences between groups in continuous variables and categorical variables, respectively. Multilevel mixed linear regression was performed to compare the Verbal Numerical Rating Scale (VNRS) and ODI Questionnaire change over the study period between both groups. A random intercept for the patients was included in the model to account for the cluster structure of the data (two-level models).

Results

In total, 54 eligible patients were enrolled and allocated in equal groups of 27. Two participants were more excluded due to wrong allocation from progressive weakness and scheduled for surgery in the T group. Consequently, 25 patients remained in the T group and 27 in the TC group as shown in [Figure 3](#).

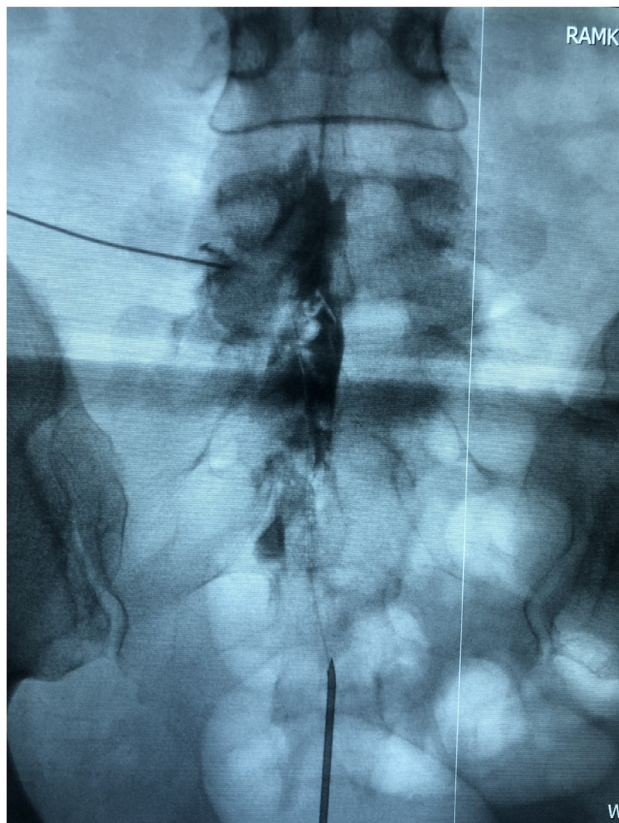


Figure 1. An anteroposterior view of contrast flow in combined supraneural transforaminal and caudal with catheter injection.

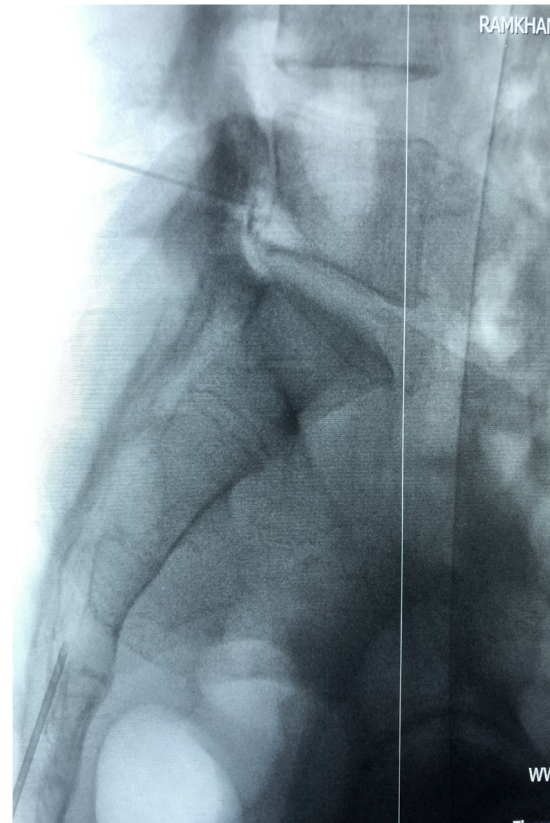


Figure 2. An lateral view of contrast flow in combined supraneural transforaminal and caudal with catheter injection.

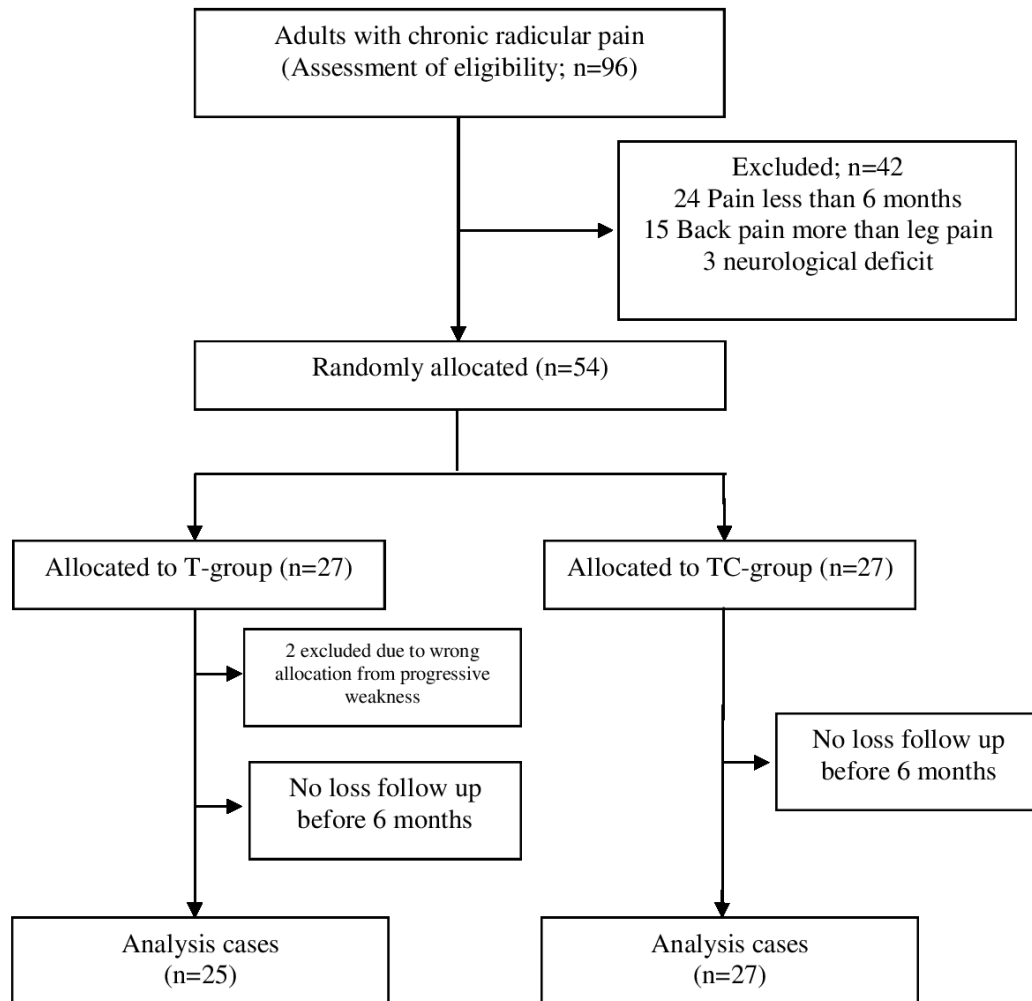


Figure 3. Flow diagram of enrolled patients.

No differences were found regarding demographic data, sex, weight, clinical diagnosis, level of pain dermatome, preprocedural VNRS and ODI before intervention as presented in [Table 1](#)¹⁸. Mean baseline VNRS was high in both groups; 74.8 ± 16.8 and 69.6 ± 15.1 in the T and TC groups, respectively.

Overall, average VNRS was significantly reduced from baseline after receiving the procedure at 1, 3 and 6 months in both groups (P -value < 0.05). However, the study showed significant differences between group comparisons at 1 and 3 months (P -value=0.009 and 0.044), respectively) as shown in [Figure 4](#)¹⁸. Moreover, average ODI was significantly improved from baseline at 1, 3 and 6 months in both groups. Nonetheless, no significant difference was found in average ODI over the study period between group comparisons ($p=0.235$) as presented in [Figure 5](#)¹⁸.

Primary outcomes

The number of patients, responding to treatment, was measured by decrease in VNRS of 30% or greater from baseline at each follow-up period, as presented in [Table 2](#)¹⁸. This study showed the TC group exhibited more patient responses to the procedure

and a significant difference than T group at 3 months follow up ($p=0.01$). However, there was no significant difference between group comparison in subgroup allocation ($p>0.05$), as shown in [Table 3](#)¹⁸. Interestingly, the TC group were more satisfied with the treatment outcome in spondylolisthesis and failed back surgery syndrome at 3 months, although not statistical significance ($p=0.07$ and $p=0.08$, respectively).

Secondary outcomes

Functional outcome assessed by the number of patients with improved ODI at least 15 points at each follow-up period showed no significant difference between groups, classified by either radicular symptoms or etiology as shown in [Table 4](#) and [Table 5](#)¹⁸.

Additionally, no serious complications, such as neurological deficit, was reported during the course of the study.

Discussion

This constituted the first prospective study to compare clinical outcomes of combined CESI to TFESI (TC group) and TFESI alone (T group) to alleviate chronic lumbar radicular pain.

Table 1. Patient characteristics at baseline.

Characteristics	T-group; n=25(%)	TC-group; n=27(%)	p-value
Gender			0.94
Male	16 (64%)	17 (63%)	
Female	9 (36%)	10 (37%)	
Age, mean (SD)	55.4 (15.7)	56.6 (15.9)	0.79
Weight, mean (SD)	67.5 (11.5)	70.1 (11.3)	0.40
Diagnosis			0.99
Disc herniation	6 (24%)	7 (26%)	
Spinal stenosis	7 (28%)	7 (26%)	
Spondylolisthesis	7 (28%)	7 (26%)	
Failed back surgery syndrome	5 (20%)	6 (22%)	
Level of pain dermatome			0.87
L4	1	2	
L5	14	15	
S1	2	1	
L4 and L5	3	5	
L5 and S1	5	4	
VNRS, mean (SD)	74.8 (16.9)	69.6 (15.1)	0.25
ODI, mean (SD)	49.2 (23.3)	44.8 (18.0)	0.44
0% - 20%	3 (12%)	0 (0%)	
21% - 40%	8 (32%)	15 (56%)	
41% - 60%	4 (16%)	6 (22%)	
61% - 80%	8 (32%)	5 (19%)	
81% - 100%	2 (8%)	1 (4%)	

This study showed combined CESI with TFESI provided more effective pain relief than TFESI separately at 3 months. Moreover, a trend was shown for higher pain relief in the TC group among spondylolisthesis patients (total of patients in the TC group compared with 3 of 7 patients in the T group) and failed back surgery syndrome (5 of 6 patients in the TC group compared with 1 of 5 the patients in the T group) at 3 months in subgroup allocation, without significant difference in which prior studies reported the mechanism of radicular pain in spondylolisthesis was usually from mechanical compression resulting in inflammatory changes in the enclosing nerve root and venous and arterial flow disability^{19,20}. Accessing the epidural space of the supraneural TFESI is relatively difficult in a severely degenerated and narrowed foramen^{13,21}. Furthermore, the injected volume of lumbar TFESI is likely to influence the results. Prior studies have reported that larger injected epidural volumes provide effective pain relief^{16,22} and a larger injected volume can lavage waste products from the epidural space, reducing the abnormal signal of the offending nerve and increasing blood flow to the ischemic nerve²³. Desai *et al.*²⁴ confirmed that the more vertebrae covered by the injected volume the better the outcome, and Furman *et al.*²⁵ commented that a larger injected volume was needed for failed back surgery patients. Unsurprisingly, the TC group showed trending toward more pain relief in spondylolisthesis and failed back surgery syndrome.

Unfortunately, this study showed the TC group experienced more significant pain relief than the T group alone at 3 months this might have been from the effect of combined techniques peaking at 3 month, then it might have gradually worn off from steroid's action, instability and the return of softened epidural adhesion and fibrosis^{15,22}

However, Friedly JL *et al.*²⁶ found epidural steroid injection plus lidocaine proposed insignificant benefit as compare with lidocaine separately in 400 patients who had lumbar central

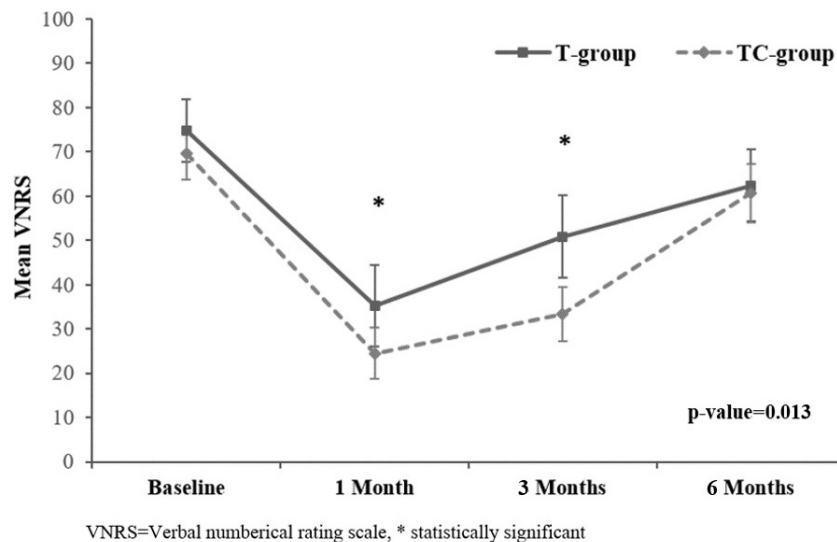


Figure 4. Average verbal numerical rating scale: between-group comparison (Line graph is presented with mean and 95%CI error bars) T group = transforaminal, TC group = transforaminal and caudal.

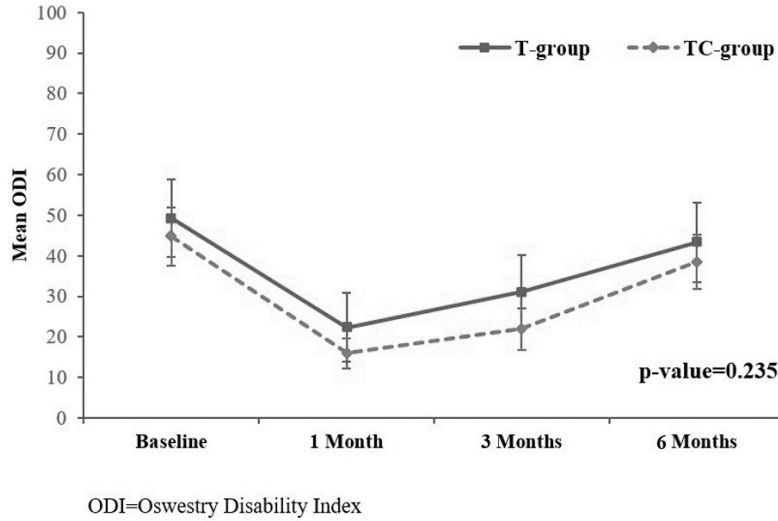


Figure 5. Average Oswestry Low Back Pain Disability Index: between-group comparison (Line graph is presented with mean and 95%CI error bars) T group = transforaminal, TC group = transforaminal and caudal.

Table 2. The number of patients with a decrease in VNRS of 30% or greater from baseline at each follow-up period in chronic lumbosacral radicular pain.

	TFESI (n=25)	TFESI+Caudal (n=27)	p-value
1 month	20 (80.0%)	25 (92.6%)	0.184
3 months	13 (52.0%)	23 (85.2%)	0.010
6 months	7 (28.0%)	7 (25.9%)	0.866

VNRS=Verbal numerical rating scale, TFESI = transforaminal epidural steroid injection, T group = transforaminal, TC group = transforaminal and caudal

spinal stenosis and moderate to severe leg pain. On the other hand, they demonstrated interlaminar or transforaminal approaches which were not exactly same techniques as this study.

Recently, a retrospective study reported combined caudal and TFESI in herniated disc provided more significant pain relief and improved patient satisfaction than only TFESI at 1 year¹⁵. In contrast, this study showed no significant pain relief between the 2 groups from herniated disc in subgroup allocation, for which demographic data of our patients with herniated disc showed lower average ages (mean age 37 ± 8.5 and 35 ± 5.4 in the T and TC groups, respectively) than a related study (mean age 62.4 ± 15.5 and 57.6 ± 15.7 in the T and TC group, respectively) in which younger patients might have received greater benefit from steroid injection in accordance with Park *et al.*²⁷ showing younger age produced a better response from TFESI. However, no significant difference was observed. Moreover, this study investigated just mild degree herniated disc such as mild unilateral paracentral disc herniation or mild foraminal stenosis and mild degree of spinal stenosis in which only the TFESI technique was sufficient to alleviate pain. Furthermore, this study injected a larger volume in the T group (3.0 ml) compared with 1.5 ml in the study of TFESI by Kircelli A *et al.*¹⁵ in which a larger injected

Table 3. The number of patients with a decrease in VNRS of 30% or greater from baseline at each follow-up period classified by etiologies.

Pain reduction	T-group (n=25)	TC-group (n=27)	p-value
Disc herniation			
1 month	6/6	7/7	NA
3 months	4/6	7/7	0.192
6 months	4/6	2/7	0.286
Spinal stenosis			
1 month	7/7	6/7	1.000
3 months	5/7	4/7	1.000
6 months	1/7	2/7	1.000
Spondylolisthesis			
1 month	5/7	7/7	0.462
3 months	3/7	7/7	0.070
6 months	1/7	2/7	1.000
Failed back surgery syndrome			
1 month	2/5	5/6	0.242
3 months	1/5	5/6	0.080
6 months	1/5	1/6	0.727

*Statistically significant VNRS=Verbal numerical rating scale, T group = transforaminal, TC group = transforaminal and caudal

volume could cover more pain generators across multiple levels of the spine in accordance with Furman *et al.*^{25,28,29}

In addition, this study postulated that synergistic anti-inflammatory effect from the double dose of steroid in the TC group

Table 4. The number of patients with improvement of Oswestry Disability Index at 15-points or greater at each follow-up period in chronic lumbosacral radicular pain.

	TFESI (n=25)	TFESI+Caudal (n=27)	p-value
1 month	16 (64.0%)	21 (77.8%)	0.273
3 months	12 (48.0%)	18 (66.7%)	0.173
6 months	7 (28.0%)	10 (37.0%)	0.488

TFESI = transforaminal epidural steroid injection

Table 5. The number of patients with improvement of Oswestry Disability Index (ODI) at 15-points or greater at each follow-up period classified by etiology.

ODI at least 15 points improvement	T-group (n=25)	TC-group (n=27)	p-value
Disc herniation			
1 month	5/6	6/7	0.906
3 months	4/6	5/7	0.853
6 months	4/6	3/7	0.391
Spinal stenosis			
1 month	5/7	5/7	1.000
3 months	2/7	2/7	1.000
6 months	0/7	1/7	0.299
Spondylolisthesis			
1 month	4/7	6/7	0.237
3 months	4/7	7/7	0.051
6 months	2/7	2/7	1.000
Failed back surgery syndrome			
1 month	2/5	4/6	0.376
3 months	2/5	4/6	0.376
6 months	1/5	4/6	0.122

T group = transforaminal, TC group = transforaminal and caudal

may have conferred better pain relief. However, one related study reported 40 mg was as effective as 80 mg of methylprednisolone in TFESI for lumbar radicular pain²⁹, while Kang *et al.*³⁰ revealed no significant difference between 10, 20 and 40 mg of triamcinolone at 1 week in TFESI for disc herniation with lumbosacral radicular pain. Unsurprisingly, this study also showed no significant difference in herniated disc concerning different dosages of corticosteroid between the 2 subgroups analysis.

Our study had several limitations. Firstly, we demonstrated radicular pain from symptomatology and physical examination, for which the source of pain may have overlapped the pain referred pattern from the zygapophysial joint, sacroiliac joint pain or enclosing soft tissues³¹⁻³³, which might have limited the efficacy of the procedure. However, many common problems are

involved in chronic low back pain. Secondly, electrodiagnosis was not performed in this study. Nonetheless, electrodiagnosis may have demonstrated false-negative findings, as demonstrated in a similar publication which showed 40 to 85% sensitivity depending on the referral range^{34,35}. Thirdly, the study did not verify anterior or posterior epidural space of contrast flow which might have affected the efficacy of the result. Fourthly, this study included a small sample size for subgroup allocation which likely underpower analysis and might not have been able to detect differences between subgroups. A larger sample size in each etiology should be demonstrated in further study. Fifthly, this study provided two different approaches, which could be increase costs of procedures. Therefore, the higher volumes should be considered if the effective result was occurred from higher volumes. Sixthly, some patients had bilateral radicular pain but only one side that more severe pain were provided in T group which might have effected for the result. Seventhly, this study did not collect exactly the duration of pain that can have huge effect on outcome as Bicket *et al.*³⁶ 's propose. However, this study included only patients who had history of lumbosacral radicular pain more than 6 months. Lastly, we did not determine whether combination effect of oral medication, physiotherapy and placebo effect which might be effect for the result.

Conclusion

The additional effect of CESI to TFESI was more effective than TFESI separately at 3 months with no neurological deficit.

Data availability

Underlying data

Figshare: data_epidural_04042020.xls. <https://doi.org/10.6084/m9.figshare.12320846.v2>¹⁸

This project contains the following underlying data:

- data_epidural_04042020.xls (Pain and disability index data for study participants. Data dictionary provided as extended data³⁶)

Extended data

Figshare: Information of abbreviation data set. <https://doi.org/10.6084/m9.figshare.12361499.v1>³⁷

This project contains the following extended data:

- Information of abbreviation data set.docx (Data dictionary)

Reporting guidelines

Figshare: CONSORT checklist for 'Effect of supranural transforaminal epidural steroid injection combined with caudal epidural steroid injection with catheter in chronic radicular pain management: double blinded randomized controlled trial' <https://doi.org/10.6084/m9.figshare.12361490>³⁸

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Open Peer Review

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Version 2

Reviewer Report 17 August 2020

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Steven Cohen

Department of Anesthesiology, Pain Medicine Division, Johns Hopkins school of medicine, Baltimore, MD, USA

The manuscript seems improved and I'm satisfied with the revision, but I would recommend an English language edit.

Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 03 August 2020

<https://doi.org/10.5256/f1000research.28023.r67927>

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Koravee Pasutharnchat

Department of Anesthesiology, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand

Thank you the authors for thoughtful responses. The revised article which states 30% or more pain relief as "clinical significant" makes the results more appropriate. Additionally, the authors have added two fluoroscopic imagings which help to determine the deposition of injectate. I appreciate the version 2 of this manuscript, making it more comprehensive and useful.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Anesthesiology and Pain management

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 29 July 2020

<https://doi.org/10.5256/f1000research.28023.r67926>

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✓ **Jatuporn Eiamcharoenwit** 

Department of Anesthesiology, Prasat Neurological Institute, Bangkok, Thailand

I agree with your revision. Clinically meaningful pain relief is defined as at least 30% reduction in pain.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Anesthesiology, Pain management

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 1

Reviewer Report 09 July 2020

<https://doi.org/10.5256/f1000research.25596.r65442>

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✓ **Abdul Hadi Mohamed** 

Department of Anaesthesiology and Critical Care, Kulliyah of Medicine, International Islamic University Malaysia, Kuantan, Malaysia

General Comments:

- This study is very relevant to today's practice and important for patients' wellbeing and continuous healthcare for low back pain with radiculopathy.

- Overall coverages and discussion are appropriate.
- The main limitation for this study is the imaging that showing the flow of contrast which determine of the deposition of steroid as well as the outcome.

Introduction:

- Adequate and covering the area of research.

Methodology:

- The selection of participants are adequate.
- I am totally agreed with the selection of a common cause of low back pain in this study.

Results:

- The table and the analysis of the result are adequate.

Discussion:

- The coverage of the discussion and suggestion are adequate.
- However, my concern with the selection of participants who is inexperienced without comparing the senior student may affect this study's strength.

References:

- Adequate

Others:

- This is a good and practical study and should be encouraged to do it multicenter.

This is a very interesting study and can give us options if we may encounter partial or temporary relief with one approach. The limitation of this study is that we can confirm that limited outcome is it due to mechanical that reduces the flow of injected since no contrast was viewed prior to injection.

Further reading

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Is the work clearly and accurately presented and does it cite the current literature?

Yes

Is the study design appropriate and is the work technically sound?

Yes

Are sufficient details of methods and analysis provided to allow replication by others?

Yes

If applicable, is the statistical analysis and its interpretation appropriate?

Yes

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

Yes

Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Author Response 12 Jul 2020

Sithapan Munjupong, Phramongkutklao Hospital and college, Bangkok, Thailand

Thank you for your review and comment.

We already edited and add more contrast flow picture as new version

Best regards

Authors

Competing Interests: No competing interests were disclosed.

Reviewer Report 08 July 2020

<https://doi.org/10.5256/f1000research.25596.r65443>

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Jatuporn Eiamcharoenwit 

Department of Anesthesiology, Prasat Neurological Institute, Bangkok, Thailand

1. The primary outcome of this study was an effective response to treatment, predefined by at least a reduced verbal numerical rating scale from baseline. If the cut-off point for the percentage of pain intensity difference was 33%, the primary outcomes may be changed. A 33% pain intensity difference is a standard of the clinically important difference in pain outcome measures.¹
2. Figure 2 and figure 3 were alternated figure legends.

References

1. Farrar J, Portenoy R, Berlin J, Kinman J, et al.: Defining the clinically important difference in pain outcome measures. *Pain*. 2000; **88** (3): 287-294 [Publisher Full Text](#)

Is the work clearly and accurately presented and does it cite the current literature?

Yes

Is the study design appropriate and is the work technically sound?

Yes

Are sufficient details of methods and analysis provided to allow replication by others?

Yes

If applicable, is the statistical analysis and its interpretation appropriate?

Yes

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: pain management

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Author Response 12 Jul 2020

Sithapan Munjupong, Phramongkutklo Hospital and college, Bangkok, Thailand

Thank you for your review and comment.

We already edited as new version

Best regards

Authors

Competing Interests: No competing interests were disclosed.

Reviewer Report 06 July 2020

<https://doi.org/10.5256/f1000research.25596.r65441>

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Koravee Pasutharnchat 

Department of Anesthesiology, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand

The authors conducted an interesting randomized study comparing transforaminal epidural steroid injection (TFESI) to TFESI combined with caudal ESI. The methodology and flow of the study were organized. The analysis was properly done and results were clear.

However, figures 2 and 3 are wrongly placed. The legends of figures state they are average verbal numerical rating scale (VNRS) and average Oswestry Low Back Pain Disability Index (ODI) respectively, while the Y-axes show ODI and VNRS, respectively.

The discussion is well written. Nevertheless, I think it would be fair if the two groups received the same total dosage of steroid, although many studies did show that two different doses of steroids did not make any differences. Another limitation of such a study, is that the patients were not blinded from their study groups would be a higher placebo effect in the group that received combined injections.

Additionally, it would be beneficial if the author had studied comparing cost-effectiveness between these two study groups.

Is the work clearly and accurately presented and does it cite the current literature?

Yes

Is the study design appropriate and is the work technically sound?

Partly

Are sufficient details of methods and analysis provided to allow replication by others?

Yes

If applicable, is the statistical analysis and its interpretation appropriate?

Yes

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Anesthesiology and Pain management

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Author Response 12 Jul 2020

Sithapan Munjupong, Phramongkutkiao Hospital and college, Bangkok, Thailand

Thank you for your review and comment.

We already edited as new version

Best regards

Authors

Competing Interests: No competing interests were disclosed.

Reviewer Report 24 June 2020

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Steven Cohen

Department of Anesthesiology, Pain Medicine Division, Johns Hopkins school of medicine,

Baltimore, MD, USA

The authors have performed a small, randomized trial comparing transforaminal epidural steroid injection (TFESI) to TFESI plus add-on caudal ESI. This is an interesting concept, there are not many randomized trials that compare add-on therapy (in essence, a comparative-effectiveness study). I enjoyed reading this and feel it would be a welcome addition to the literature.

Introduction:

1. Introduction, para 1: Steroids also suppress ectopic discharges of injured nerves, and may enhance the washout of inflammatory cytokines. This is eloquently noted in the discussion but should be noted at the beginning of the introduction as well.
2. The authors use the term synergistic incorrectly. Synergistic would be $20\% + 20\% = 50\%$, but while 2 treatments may afford better results than a single one (see Gilron *et al.* studies for neuropathic medications), the results are usually not even additive.
3. There is a downside to doing a caudal + TFESI even if it works better. There are 2 different billing codes, so it may not be approved. Not only does it increase costs, but it also increases the risk (compared to just using higher volumes or doses). The authors should, therefore, provide a rationale as to why the combination should work better (the background on the literature is otherwise focused and to the point).
4. Please consider providing objectives in the 'introduction' (the authors do a good job of setting the stage for the study, but specific objectives would be helpful).

Methods:

1. I actually like the fact that there was no minimum pain score, as this is always subjective and when a minimum is employed, patients often end up skewed towards the cutoff (i.e. a non-normal curve).
2. On a similar note, I also appreciate that patients with both a herniated disc and spinal stenosis. Were there any differences in outcomes?
3. Many patients with radicular pain have bilateral symptoms. If this were the case, how did the investigators choose what side to inject? Or were these patients excluded (if this is the case, please note it in the 'methods')?
4. Why did a nurse anesthetist assess outcomes? Was sedation used (please mention)?
5. Although the authors performed a power analysis, the study is likely underpowered, as well-designed studies now enroll several hundred people (see Friedly *et al.* NEJM, FDA-endorsed CLEAR study) to detect a difference between an ESI and a sham injection, so comparing 2 different ESI should require even more. Yet, the authors have shown a difference.
6. Please consider mentioning the randomization block size.
7. The study had excellent retention (few lost-to-follow-ups), but please note how missing data were handled in the 'statistical analysis' section.

Results:

1. I agree with one categorical outcome being $\geq 50\%$ pain relief, but the IMMPACT guidelines state that 30% or more relief is 'clinically meaningful', so most pain studies now use that cutoff as a positive outcome. According to a review by Bicket MC *et al.* in Pain Pract 2017, an even lower percentage of pain relief seems to predict satisfaction in most patients. So you might consider showing the proportion of people who also obtained $\geq 30\%$ pain relief.
2. Duration of pain is a really important clinical variable that can have a huge effect on outcome (Bicket *et al.* AQUARIUS.. Reg Anesth Pain Med 2018). Please note the duration of pain for the groups.
3. Figures 2 and 3 are wrong because the figure legends states they are showing pain scores & ODI respectively when the y-axes state they are showing ODI and pain scores, respectively (i.e. they're reversed).

Discussion: - in general, well-written and focused.

1. There are 2 possible reasons that warrant mention as to why a difference was shown. One is that the combination group received a higher dose of steroid and local anesthetic (if there had been a group that received a higher dose of steroids by one route as a control that would have formed another control and answered questions). However, there are half a dozen studies that compare 2 different doses of steroids and nearly all have found no difference.

The second reason is that the group that received both injections had greater expectations, and therefore had a higher placebo response rate.

Is the work clearly and accurately presented and does it cite the current literature?

Yes

Is the study design appropriate and is the work technically sound?

Partly

Are sufficient details of methods and analysis provided to allow replication by others?

Yes

If applicable, is the statistical analysis and its interpretation appropriate?

Yes

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Pain Medicine

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 12 Jul 2020

Sithapan Munjpong, Phramongkutkiao Hospital and college, Bangkok, Thailand

Thank your so much Dr.Cohen for your review and comment.

We already revised the manuscript in Version 2 and have changed the definition of pain relief from 50% to 30%, the conclusion was changed in the subgroup analysis.

All of nurse in our clinic are nurse anaesthetists. Therefore, only one nurse anaesthetist was trained to evaluated the outcome. However, the patients had not been sedated.

Furthermore, we performed other answers in the revised version.

Best regards

Authors

Competing Interests: No competing interests were disclosed.

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