ORIGINAL ARTICLE

54

COMPARISON OF SUBPEDICULAR AND KAMBIN'S TRIANGLE APPROACHES IN TRANSFORAMINAL EPIDURAL INJECTION APPLICATIONS IN CASE OF LUMBAR DISC HERNIA

Bilal Aykaç, Abdullah Küçükalp

Private Hayat Hospital, Clinic of Orthopedics and Traumatology, Bursa, Turkey

Objective: The lumbar transforaminal epidural steroid injection (LTFESI) procedure has been used safely in patients with radiculopathic pain secondary to lumbar disc herniation, who did not respond to conservative treatment for many years. In this study, we show that the approach using the Kambin's triangle area is an effective and reliable method of application, as an alternative to the subpedicular approach commonly used in LTFESI.

Materials and Methods: Between 2017-2021, 79 patients with symptoms of radiculopathy due to lumbar disc herniation, confirmed by clinical and radiological diagnosis, were included in the study. To the patients: In the operating room, Kambin's triangle in 43 patients and subpedicular approaches in 36 patients were performed with LTFESI, accompanied by scopy image. For radiculopathic pai, Numerical Rating Scale (NRS) and functionally Oswestry Disability Index (ODI) scores were statistically compared in two different approaches before the procedure, at the 2nd week and 3rd month after the procedure.

Results: There was no significant difference between the two groups in pre-procedural NRS (p=0.240) and ODI (p=0.517) scoring. It was determined that the change observed in NRS and ODI measurements over time in both approaches showed a statistically significant difference in response to treatment (NRS; p=0.008, ODI; p=0.016). There was no significant difference between the two groups after the procedure, between the NRS (p=0.523) and ODI (p=0.617) scores at the 2nd week and the NRS (p=0.058) and ODI (p=0.056) scores at the 3rd month. Relative treatment effects were found to be similar in the subpedicular and Kambin's triangle groups.

Conclusion: It has been shown that the Kambin's triangle area, which is poorer in terms of neurovascular structures, can be used effectively and safely as an alternative to the subpedicular area in LTFESI applications.

Keywords: Transforaminal injection, Kambin's triangle, subpedicular area, lumbar disc herniation

INTRODUCTION

In cases of lumbar disc herniation, leg pain is one of the most common complaints because of the pressure on the herniated disc material on the nerve roots. Additionally, numbness and loss of strength can be seen in the dermatomes and myotomes of the relevant nerve roots in the lower extremities⁽¹⁾. Although this may adversely affect the quality of life of patients, they can create great burdens for national economies. The first choice in treatment is conservative treatment methods^(2,3).

In cases where conservative treatment is ineffective, minimally invasive interventional treatments have been used more and more frequently. Among them, the transforaminal epidural steroid injection (TFESI) procedure has been used for many years for treating radiculopathy secondary to lumbar disc herniation⁽²⁾. These procedures are effective and safe in relieving pain. Indications, evidence, and safety considerations for the technique have been identified⁽⁴⁾.

The most commonly used method in lumbar TFESI (LTFESI) is the subpedicular approach. In the subpedicular approach, cases of spinal cord infarction secondary to neurovascular injury, which is a rare but catastrophic complication, have been reported⁽⁵⁾. The Kambin's triangle approach is as effective as the subpedicular approach and offers significant advantages in terms of avoiding neurovascular complications⁽⁶⁾.

In this study, we show that the Kambin's triangle approach, which uses the Kambin's triangle area, which is defined as the safe zone, is an effective and reliable application method as an alternative to the subpedicular approach, which is open to complications in LTFESI.

MATERIALS AND METHODS

Study Group

Ethics committee approval was obtained for this study, dated 16.06.2021 and numbered 2011-KAEK-26/383 of the Bursa

Address for Correspondence: Bilal Aykaç, Private Hayat Hospital, Clinic of Orthopedics and Traumatology, Bursa, Turkey Phone: +90 505 622 99 85 **E-mail:** draykac@gmail.com **Received:** 09.01.2023 **Accepted:** 23.02.2023 **ORCID ID:** orcid.org/0000-0002-6180-2467



[®]Copyright 2023 by the Turkish Spine Society / The Journal of Turkish Spinal Surgery published by Galenos Publishing House. Licensed by Creative Commons Attribution-NonCommercial 4.0 International (CC BY-NC-ND 4.0).

turkishspine

Uludağ University Ethics Committee. All the patients were selected from patients who had previously received medical treatment and/or physical therapy protocol treatment, but did not have a clinical response. Patients with a history of previous lumbar surgery, degenerative spinal stenosis, surgical indication, bleeding diathesis, morbid obesity (body mass index over 40), local skin lesion, previous history of LTFESI, and patients under 18 years of age were excluded from the study. Between 2017 and 2021, 84 patients, who were confirmed by clinical and radiological diagnosis, had lumbar disc herniation in magnetic resonance imaging taken at least 3 months before the procedure, had radiculopathy symptoms due to lumbar disc herniation, had no acute neurological symptoms, and motor loss, were followed up and scored. (Two patients without follow-up and 3 patients with more than one level of LTFESI were excluded from the study) 79 patients were included in the study.

Process Preparation and Technique

Informed consent forms were obtained from all patients before the LTFESI procedure. Level detection was performed in the operating room, on the surgical table, by monitoring, in the prone position, under scopy control. After sterilization of the area to be injected, 5 cc of 2% prilocaine hydrochloride was injected as a local anesthetic. Subsequently, the posterolateral transforaminal area was accessed with a 22 gauge spinal needle under scopy control, accompanied by antero-posterior (AP) and lateral (L) scopy images. By determining the Kambin (Figure 1A) in 43 patients, the subpedicular area (Figure 1B) in 36 patients, and controlling the needle position with L images (Figure 2) to prevent needle trauma to the root and disc after AP, 1 cc opaque material was again accompanied by AP scopy image. Iohexol was diluted with 5 cc of isotonic solution and approximately 1.5-2 cc was injected for confirmation (Figure 3). After defining the dural border (descending root), foramen, and root structures emerging from the foramen in the medial, a total of 5 cc was applied by mixing 1 cc betamethasone and 4 cc 2% prilocaine hydrochloride (Figure 4). During the procedure,



active foot movements were checked for severe leg pain and possible motor deficit, keeping in contact with the patient. After the procedure, the patients were followed up for at least 3 h, and they were mobilized and discharged after the motor-sensory block was completely over. Numerical Rating Scale (NRS) scores for pain level and Oswestry Disability Index (ODI) scores for functional evaluation were examined before the procedure, at the 2nd week and at the 3rd month after the procedure, from the files of the patients who underwent LTFESI. Considering the anatomical limits of the patients, according to the injection application area: They were collected in two different groups, namely the Kambin's triangle and the subpedicular area, and their scores were compared.

Statistical Analysis

The distributions of age, NRS, and ODI were examined using Shapiro-Wilk's tests, normality plots, and skewness/kurtosis statistics. Since none distributed normally, they were provided by a median [interquartile range (IQR): 1st quartile-3rd quartile]. Mean ± standard deviation was also reported for NRS and ODI. Frequency and proportion were given for sex.

The age and sex of the patients were compared between application groups by Mann-Whitney U test and Pearson chisquare test, respectively. NRS and ODI were compared between application groups at each evaluation period by Mann-Whitney U test, as well. The changes in NRS and ODI measurements across time were compared between application groups by F1-LD-F1 design. ANOVA type test statistics, the degree of freedom, and p-values were reported for the overall time effect and group*time interaction effects. Relative treatment effects (RTEs) were provided with 95% confidence interval by graphs. A p-value<0.05 was considered as statistically significant. Descriptive statistics were calculated using IBM SPSS Statistics 22.0 (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.). The F1-LD-F1 design was performed using the RStudio software (v.1.4.1106)⁽⁷⁾ and the nparLD package⁽⁸⁾ in the R v.4.1 programming language⁽⁹⁾.



Figure 1. Application areas accompanied by AP scope; **A)** Kambin's triangle area, **B)** Subpedicular area AP: Antero-posterior



RESULTS

Seventy nine patients who met the criteria and followed up were included in the study. The median age of the patients was 46 years (IQR: 35-61) in the group in which the Kambin's triangle approach was applied, while it was 48 years (IQR: 39-61) in the subpedicular approach group. 53.5% (n=23) of the group in which the Kambin's triangle approach was applied and 63.9% (n=23) of the group in which the subpedicular approach was applied were women. There was no statistically significant difference between the two groups in terms of age and gender (p=0.668 for age, p=0.351 for gender).

When the pain and disability levels of the patients were examined, the median NRS was 8 (IQR: 7-8) before treatment for both groups. The median NRS was determined as 2 (IQR: 1-3) at weeks 2 and 2 (IQR: 0-3) at 3 months in the group in which the Kambin's triangle approach was applied. In the subpedicular approach group, the median NRS was 2



Figure 2. The position of the needle in the scope image in the Kambin area



Figure 3. AP image with opaque material injection AP: Antero-posterior

(IQR: 1-4) at the 2nd week and 3rd month (Table 1). There was no significant difference between the pre-procedural NRS (p=0.240) and ODI (p=0.517) scores between the two groups. The change observed in NRS and ODI scores over time showed a statistically significant difference in both approaches; a significant improvement was observed in NRS pain (Figure 5) and ODI functional (Figure 6) scoring (NRS; p-value=0.008 ODI; p-value=0.016). When both groups were compared: There was no significant difference between the NRS (p=0.523) and ODI (p=0.617) scores at the post-procedure 2nd week, and the NRS (p=0.058) and ODI (p=0.056) scores at the 3rd month (Table 2). When RTEs were examined, it was found that both pain and disability levels decreased significantly in the 2nd week, but increased slightly in the 3rd month in the subpedicular group; in the Kambin's triangle group, it was observed that the decrease in the level of pain and disability continued, albeit slightly, at the 3rd month. However, the RTEs of the two groups at each time point were similar (Figure 7).

DISCUSSION

TFESI has been used for many years for treating radiculopathy caused by lumbar disc herniation⁽²⁾. LTFESI is a targeted therapy tool for lumbar radiculopathy with up to 80% immediate response⁽¹⁰⁾. There is strong evidence to support the use of lumbar TFESI in patients with acute to subacute, unilateral radicular pain caused by herniated nucleus pulposus^(11,12). The most commonly used approach for transforaminal injections is the subpedicular application technique⁽¹³⁾, first described by Bogduk and Endres⁽¹⁴⁾. Some authors are; declaring that the subpedicular approach to transforaminal epidural injections is actually unsafe, he believes that when administering LTFESI, they should be made in the lower part of the foramen, known as the Kambin's triangle, where the vascular and nerve structures are less dense⁽¹⁵⁾. In our study, the subpedicular area was determined in 36 patients and LTFESI was applied. To



Figure 4. After the application of opaque material, local anesthetic and steroid injection and spread image in the AP plane AP: Antero-posterior



minimize possible complications and considering the literature supporting this study, LTFESI was applied to 43 patients with the Kambin's triangle approach. In the two patient groups (Table 2), in which there was no significant difference between preprocedural NRS and ODI scores, NRS and ODI scores decreased significantly at the 2nd week and 3rd month after the procedure (Figures 5, 6).

Sencan et al.⁽¹⁶⁾, in their study on 61 patients, applied subpedicular injection to the patients. They measured the NRS scores of patients who had a mean NRS of 8 before the procedure at the 1st week, 2nd week, and 3rd month after the procedure, respectively, as 0.3,3. Likewise, they measured their ODI score, which was 48 before the procedure, to 26, 22, 22 at the 1st week, 2nd week, and 3rd month after the procedure, respectively. They obtained significant statistical data toward improvement in NRS and ODI scores in subpedicular area applications and as a result; They stated that the application of subpedicular LTFESI is an effective and safe method for radiculopathy. In our study, we applied subpedicular LTFESI to 36 of 79 patients. In our evaluation: In patients with a mean NRS score of 8 before

the procedure, the postoperative 2^{nd} week and 3^{rd} month scores were found to be 2.2, respectivel; similarly, in patients with a pre-procedural ODI score of 71, the postoperative 2^{nd} week and 3^{rd} month scores were 14.19, respectively found.

Ghai et al.⁽¹⁷⁾ applied subpedicular to 38 of 75 patients and Kambin to 37 of them in their randomized controlled study; when they compared both groups, they found statistically similar results in NRS and ODI scores at 2nd week, 1st month, and 3rd month and stated that both applications could be used safely for radiculopathy. In our study, in patients with similar demographic data, pain and functional score before the procedure; we observed that both treatments were effective in terms of improvement in pain and functional scores, and the RTS values were similar.

Complications from these procedures result from needle insertion and/or drug administration. Potential risks include infection, hematoma, intravascular drug injection, direct nerve trauma, subdural drug injection, air embolism, disc space entry, urinary retention, and hypersensitivity reactions⁽¹²⁾.

Table 1. Patients' pain and disability levels through time with respect to the application				
	Application			
	Kambin's triangle (n=43)	Subpedicular (n=36)		
NRS [median (IQR)]				
Baseline	8 (7-8)	8 (7-8)		
2 nd week	2 (1-3)	2 (1-4)		
3 rd month	2 (0-3)	2 (1-4)		
ODI [median (IQR)]				
Baseline	77 (67-78)	71 (67-77)		
2 nd week	14 (12-28)	14 (10-33)		
3 rd month	14 (4-26)	19 (9-40)		

NRS: Numeric Rating Scale for pain, ODI: Oswestry Disability Index, IQR: Interquartile range, 1st quantile-3rd quantile



Figure 5. Distribution of NRS values within each application NRS: Numerical Rating Scale



Figure 6. Distribution of ODI values within each application ODI: Oswestry Disability Index



	Application	Application		
	Kambin's triangle (n=43)	Subpedicular (n=36)	p-value	
NRS				
Baseline	7.81±15.62 8 (7-8)	7.56±15.30 8 (7-8)	0.240	
2 nd week	2.26±1.51 2 (1-3)	2.53±1.75 2 (1-4)	0.523	
3 rd month	2.07±2.02 2 (0-3)	3.00±2.27 2 (1-4)	0.058	
ODI				
Baseline	74.42±7.44 77 (67-78)	72.81±7.62 71 (67-77)	0.517	
2 nd week	18.93±14.45 14 (12-28)	22.81±17.45 14 (10-33)	0.617	
3 rd month	18.12±19.55 14 (4-26)	27.06±22.60 19 (9-40)	0.056	

Table 2. Patients' pain and disability levels through time with respect to the application

NRS: Numeric Rating Scale for pain, ODI: Oswestry Disability Index, SD: Standard deviation NRS and ODI were reported as mean \pm SD and median (IQR)



Figure 7. Relative treatment effect of pain and disability levels based on application

RTE: Relative treatment effect, ODI: Oswestry Disability Index

Windsor et al. ⁽¹⁸⁾ reported that severe infections are rare with an incidence of 0.1-0.01% of all spinal injections. Cases of meningitis, epidural abscess, osteomyelitis, and discitis have been reported. *Staphylococcus aureus* is the most common organism. It is believed to be administered through the skin through the pinhole. Although these risks are valid for both application areas, no complications related to infection were observed in our series. The incidence of epidural hematoma is estimated to be less than 1 in 150,000 epidural applications⁽¹⁹⁾. Damage to the underlying vessels can lead to hematomas that cannot be visualized with conventional fluoroscopy⁽¹²⁾. However, Murthy et al.⁽²⁰⁾ reported that the Adamkiewicz artery (AKA) passes through the safe triangle and that the injection applied to this region may directly damage the vein. In the study, 97% of the AKA foramen were located in the upper half (88% in the upper third, 9% in the middle third) and 2% in the lower third. He reported that AKA was never seen in the lower fifth of the foramen. Glaser and Shah⁽¹⁵⁾ stated that AKA can enter any middle thoracic, lower thoracic, or lumbar foramen, and the exact level cannot be known by the procedural specialist. The authors reported that the subpedicular approach to transforaminal epidural injections is unsafe and stated that injury to the AKA may cause paraplegia. Therefore, they argued that as an alternative to subpedicular administration, catastrophic injury could be avoided and transforaminal injections should be made in the lower part of the foramen known as the Kambin's triangle.

Direct trauma with the needle to the spinal nerve or dorsal root ganglion is another complication of accidental needle insertion, particularly when performing TFESI. Severe pain occurs with this trauma, and it is important not to over-sedation in order not to mask the complication⁽¹⁴⁾. For this reason, we performed the procedures by keeping in touch with the local application, without applying sedation to our patients during the application. Neurological complications were not observed in any of our patients.

It is important to recognize the pattern of subdural and subarachnoid contrast diffusion during the application of the LTFESI procedure⁽²¹⁾. If local anesthetics are injected intrathecally, blockade of neural elements may cause the central canal, cauda equina, and conus medularis syndromes depending on penetration and level of blockage. The transient



respiratory depression increased weakness/sensory loss, apnea, and loss of consciousness may also occur, and these are said to be associated with increased subdural spread of anesthetics^(21,22). Other complications include persistent paresthesias, arachnoiditis, and meningitis. The amount of local anesthetic (6-8 mL) typically used in lumbar epidural injections is usually not sufficient to cause respiratory depression. However, a greater volume in the subdural space can rapidly increase in the head direction, causing serious cardiovascular and respiratory effects^(22,23). In this study, a contrast material spread pattern was observed in scopy vision in all patients, and LTFESI was applied after ensuring that there was no intrathecal spread, and the mentioned complications were not observed in either group.

Levi et al.⁽²⁴⁾ in their review study including the Kambin's triangle application, they reported that 12 of 257 patients had intradiscal injections, 8 had intrathecal injections, and 17 had vascular injections, and they stated that there were no neurological complications in any patient. Ghai et al.⁽¹⁷⁾ in their randomized controlled study, they reported that 7 of 37 patients who underwent the Kambin's triangle approach developed intravascular access and 7 developed needle paresthesia. They reported that 4 of 38 patients who underwent a subpedicular approach developed intravascular access and 6 developed needle paresthesia. In our study, no complications were observed in either group. We believe that the LTFESI application was applied to a selected patient group, sedation was not given during the application, repetitive scopy imaging in both planes during needle placement, and contrast material administration helped us avoid related complications.

Complications from lumbar epidural injections are extremely rare. Many, if not all, complications can be avoided with the utmost attention to sterility, correct needle placement, and a thorough understanding of the involved anatomy and contrast medium diffusion on fluoroscopic imaging.

Study Limitations

In this study; the limitations of the study are the lack of a sufficient number of patients for evaluating disc degeneration, the inability to measure the amount of radiation exposed in fluoroscopy-guided practice, and the lack of long-term follow-up.

CONCLUSION

In our study, it was observed that the Kambin's triangle application can be applied as effectively and safely as the subpedicular application. Case reports reporting that the subpedicular area, which is commonly used in LTFESI applications, is open to complications, have been presented in the literature. These complications arise from the anatomically rich area of neurovascular structures. Although complications were not observed in either group in our study, we think that the anatomically defined Kambin's triangle area, which is poorer in terms of neurovascular structures, can be used safely as an alternative.

Ethics

Ethics Committee Approval: Ethics committee approval was obtained for this study, dated 16.06.2021 and numbered 2011-KAEK-26/383 of the Bursa Uludağ University Ethics Committee. **Informed Consent:** Informed consent forms were obtained from all patients before the LTFESI procedure.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: B.A., Concept: B.A., A.K., Design: B.A., A.K., Data Collection or Processing: B.A., A.K., Analysis or Interpretation: B.A., A.K., Literature Search: B.A., Writing: B.A., A.K.

Conflict of Interest: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study received no financial support.

REFERENCES

- 1. Khan AN, Jacobsen HE, Khan J, Filippi CG, Levine M, Lehman RA Jr, et al. Inflammatory biomarkers of low back pain and disc degeneration: a review. Ann N Y Acad Sci. 2017;1410:68-84.
- 2. He Y, Chen L, Xu Z, Wang L, Liu B. Lumbar transforaminal epidural block for treatment of low back pain with radicular pain. Nan Fang Yi Ke Da Xue Xue Bao. 2020;40:1804-9.
- Thompson J, Merrill RK, Qureshi SA, Leven DM. Compression of the S1 Nerve Root by an Extradural Vascular Malformation: A Case Report and Discussion of Atypical Causes of Lumbar Radiculopathy. Int J Spine Surg. 2020;14:96-101.
- 4. Rivera CE. Lumbar Epidural Steroid Injections. Phys Med Rehabil Clin N Am. 2018;29:73-92.
- Ignjatovic S, Omidi R, Kubik-Huch RA, Anderson S, Ahlhelm FJ. The retroneural approach: an alternative technique for lumbar transforaminal epidural steroid injections. Acta Radiol. 2018;59:1508-16.
- Park JW, Nam HS, Cho SK, Jung HJ, Lee BJ, Park Y. Kambin's Triangle Approach of Lumbar Transforaminal Epidural Injection with Spinal Stenosis. Ann Rehabil Med. 2011;35:833-43.
- RStudio Team (2021). RStudio: Integrated Development Environment for R. RStudio, PBC, Boston, MA. Available from: URL: http://www. rstudio.com/
- Noguchi K, Gel YR, Brunner E, Konietschke F. nparLD: An R Software Package for the Nonparametric Analysis of Longitudinal Data in Factorial Experiments. JSS. 2012;50:1-23.
- 9. R Core Team. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. 2021
- Leung SM, Chau WW, Law SW, Fung KY. Clinical value of transforaminal epidural steroid injection in lumbar radiculopathy. Hong Kong Med J. 2015;21:394-400.
- 11. Ng L, Chaudhary N, Sell P. The efficacy of corticosteroids in periradicular infiltration for chronic radicular pain: a randomized, double-blind, controlled trial. Spine. 2005;30:857-62.
- 12. Goodman BS, Posecion LW, Mallempati S, Bayazitoglu M. Complications and pitfalls of lumbar interlaminar and transforaminal epidural injections. Curr Rev Musculoskelet Med. 2008;1:212-22.
- 13. Viswanathan VK, Kanna RM, Farhadi HE. Role of transforaminal epidural injections or selective nerve root blocks in the management



of lumbar radicular syndrome - A narrative, evidence-based review. J Clin Orthop Trauma. 2020;11:802-9.

- 14. Bogduk N, Endres SM. fourth ed. Clinical Anatomy of the Lumbar Spine and Sacrum. Elsevier/Churchill Livingstone; New York: 2005.
- 15. Glaser SE, Shah RV. Root cause analysis of paraplegia following transforaminal epidural steroid injections: the 'unsafe' triangle. Pain Physician. 2010;13:237-44.
- Sencan S, Celenlioglu AE, Yazici G, Gunduz OH. Transforaminal Epidural Steroid Injection Improves Neuropathic Pain in Lumbar Radiculopathy: A Prospective, Clinical Study. Neurol India. 2021;69:910-5.
- 17. Ghai B, Gupta AK, Makkar JK, Dhatt SS, Contrast Medium Volume Needed to Reach Anterior Epidural Space via the Kambin Triangle or Subpedicular Approach for Transforaminal Epidural Injection. Pain Physician. 2020;23:383-92.
- Windsor RE, Storm S, Sugar R. Prevention and management of complications resulting from common spinal injections. Pain Physician. 2003;6:473-83.
- 19. Horlocker TT, Wedel DJ, Benzon H, Brown DL, Enneking FK, Heit JA, et al. Raview Regional anesthesia in the anticoagulated patient:

defining the risks (the second ASRA Consensus Conference on Neuraxial Anesthesia and Anticoagulation). Reg Anesth Pain Med. 2003;28:172-97.

- 20. Murthy NS, Maus TP, Behrns CL. Intraforaminal location of the great anterior radiculomedullary artery (artery of Adamkiewicz): a retrospective review. Pain Med. 2010;11:1756-64.
- Goodman BS, Bayazitoglu M, Mallempati S, Noble BR, Geffen JF. Dural puncture and subdural injection: a complication of lumbar transforaminal epidural injections. Pain Physician. 2007;10:697-705.
- 22. Chauhan S, Gaur A, Tripathi M, Kaushik S. Unintentional combined epidural and subdural block. Case report. Reg Anesth. 1995;20:249-51.
- Mizuyama K, Dohi S. An accidental subdural injection of a local anaesthetic resulting in respiratory depression. Can J Anaesth. 1993;40:83-4.
- 24. Levi D, Horn S, Corcoran S. The Incidence of Intradiscal, Intrathecal, and Intravascular Flow During the Performance of Retrodiscal (Infraneural) Approach for Lumbar Transforaminal Epidural Steroid Injections. Pain Med. 2016;17:1416-22.