Anesth Pain Med. 2018 August; 8(4):e74124. doi: 10.5812/aapm.74124.

Published online 2018 July 29. **Research Article**

An Evaluation of the Adding Magnesium Sulfate to Ropivacaine on Ultrasound-Guided Transverse Abdominis Plane Block After Abdominal Hysterectomy

Farnad Imani [1,*], Poupak Rahimzadeh [1], Hamid-Reza Faiz [2] and Alireza Abdullahzadeh-Baghaei [3]

[1] Pain Research Center, Iran University of Medical Sciences, Tehran, Iran
[2] Anesthesiology Department, Iran University of Medical Sciences, Tehran, Iran
[3] Anesthesiology, Critical Care and Pain Management Research Center, Hormozgan University of Medical Science, Bandarabbas, Iran

[*] *Corresponding author*: Pain Research Center, Rasoul Akram Medical Center, Iran University of Medical Sciences, Tehran, Iran. Tel: +98-66515758, Email: farnadimani@yahoo.com

Received 2018 April 30; **Revised** 2018 June 10; **Accepted** 2018 June 13.

Abstract

Background: Post-hysterectomy pain is extremely annoying and using transverse abdominis plane (TAP) block can be a useful method to manage postoperative pain, but its duration of effect is challenging. Magnesium sulfate increases, in some cases, the effects of local anesthetics on the peripheral nerve blocks.

Objectives: The current study aimed at investigating the effects of adding magnesium sulfate to ropivacaine in the transverse abdominis plane block after hysterectomy.

Methods: The current randomized, double blind, clinical trial, to manage postoperative pain, was conducted on a total of 60 patients, 30 - 60 years old, ASA (American Society of Anesthesiologists) class I-II undergone elective abdominal hysterectomy candidates to receive ultrasound-guided bilateral transverse abdominis abdominis plane (TAP) blocks. Patients with coagulation disorders, infection, history of any addiction, sensitivity to the local anesthetics and magnesium sulfate were excluded. The subjects were equally allocated into two groups, the control group, ropivacaine plus normal saline (R), and the study group, ropivacaine plus magnesium sulfate (RM). The injection contained 19 mL ropivacaine 0.2% plus 1 mL normal saline in the group R, and 19 mL ropivacaine 0.2% plus 1 mL magnesium sulfate 50% in the RM group on each side. As well as the patients' characteristics, the level of pain score (visual analogue scale = VAS), rescue analgesic demand (diclofenac suppository), and possible adverse effects were evaluated at 1, 2, 6, 12, and 24 hours after the operation in the two groups.

Results: The mean pain scores of the patients at the first hour after surgery were 5.7 ± 0.9 and 5.9 ± 1.1 in R and RM groups, respectively. The scores reached 2.9 ± 0.5 and 2.7 ± 0.4 at the second hour after surgery (the first post-block measurement) and 3.1 ± 0.7 and 2.8 ± 0.7 within the next 24 hours, respectively. Although the pain scores were generally lower at all hours in the RM group, none was statistically significant. The rescue analgesic consumption gradually increased in the two groups, and it was less in the study group than in the control group in the first hours after the block (second hour after surgery); however, it was not statistically significant. No adverse effects were observed in the two groups.

Conclusions: Results of the current study suggested that the addition of magnesium sulfate to ropivacaine in TAP block does not affect the post-hysterectomy pain.

Keywords: Magnesium Sulfate, Postoperative Pain, Ropivacaine, Transverse Abdominis Plane Block

1. Background

After cesarean section, hysterectomy is considered the second most common gynecological surgery in females (1). Post-hysterectomy pain is one of the postoperative complications. Pain along with nausea, vomiting, and drowsiness, is one of the three most common causes of patients' delayed discharge (2). A variety of techniques are used to provide better pain management outcome, including systemic analgesics, patient-controlled analgesia, and peripheral analgesic procedures (3, 4). Opioids administration is associated with several systemic complications. Thus, inclination to perform peripheral analgesic procedures such as transverse abdominis plane block is recently increased (5-7).

This type of block is studied for its effectiveness in pain management in various surgical procedures such as cesarean section, hysterectomy, prostatectomy, colonic surgery and laparoscopy, and even in surgical procedures in children (8-14). Transverse abdominis plane (TAP) block was even performed alone in a case of a high-risk elderly patient undergoing gastric operation (15). In addition to the

proper technique, the duration of analgesia in this block is influenced by the pharmacokinetics of the administered drugs. Various measures, such as catheter placement in site and use of adjuvant drugs are raised to prolong the effect of the block (16-18). The impact of systemic magnesium sulfate on postoperative pain management is evaluated in various studies (19, 20).

2. Objectives

The current study aimed at evaluating the effects of adding Magnesium sulfate to ropivacaine in the TAP block after hysterectomy and the possible ensuing complications and adverse effects.

3. Methods

In a randomized, double-blind, clinical trial, a total of 60 patients, 30 - 60 years old, ASA (American Society of Anesthesiologists) class I-II, candidates for hysterectomy under general anesthesia were enrolled in the study, following the verbal explanation of the procedure and details, and obtaining informed consent. Patients with coagulation disorders, infection, history of any addiction, sensitivity to the local anesthetics and magnesium sulfate were excluded. Patients were anesthetized with 2 mg midazolam and 2 μg/kg Fentanyl, 2 mg/kg propofol, and 0.5 mg/kg atracurium. Anesthesia was maintained with 100 μg/kg/minute propofol in addition to O_2 and N_2O. After the procedure, 2.5 mg neostigmine and 1.25 mg atropine were injected as reverse of neuromuscular relaxants. After recovering from anesthesia, the patients were randomly divided into two groups of study (RM) and control (R) and underwent bilateral ultrasound-guided TAP block. In the study group (RM), 19 mL ropivacaine 0.2% (Naropin 1%, AstraZeneca, France) in combination with 1 mL magnesium sulfate (500 mg) (Pasteur Institute, Iran), and in the control group (R) 19 mL ropivacaine 0.2% in combination with 1 mL normal saline 0.9% were injected. The block was performed in recovery room under cardiac, blood pressure, and heart rate monitoring with ultrasound guidance (SonoSite S-Nerve ultrasound machine) by a well-qualified physician, unaware of the type of the solution to be injected. To perform the block, the patients were placed in supine position. The needle (Pajunk, Germany, 22G, 80 mm, visible to ultrasound) insertion point was between the mid and anterior axillary line, below the rib line extending to the iliac prominence, at the same level of the abdominal wall incision. A linear probe of a frequency between 6 - 15 MHz and an in-plane needle insertion technique were used in this block.

Using the visual analog scale (VAS), the patients' pain both in rest and with movement was measured and recorded, from 0 to 10 (0 for no pain and 10 for severe unbearable pain), at 1, 2, 6, 12, and 24 hours after the surgery by another person, without knowledge of group assignment. If a patient reported a VAS pain score of greater than 3, rescue analgesic (diclofenac suppository 100 mg) was given. Rescue analgesic consumption, complications, patients' characteristics, and results were recorded on a questionnaire. The data were analyzed with SPSS version 18. The quantitative and qualitative data were evaluated using independent t and chi-square tests, respectively, and the P value of less than 0.05 was considered statistically significant.

4. Results

The patients' characteristics in the two groups (age and weight) were not significantly different (Table 1). Based on the VAS scale, the mean pain score of the patients in both groups at the first hour after surgery (before the block) was above 5, which indicated no significant difference between the two groups, but decreased gradually thereafter and at the 24-hour it reached 3.1 and 2.8 in the control and study groups, respectively. Although the mean pain score was less in the study group than in the control group at all hours of the study, there was no significant difference regarding the rate of pain score between the two groups (Table 1). The amount of rescue analgesic consumed (diclofenac suppository) gradually increased during the study hours until it reached its highest level at 12 hours; no significant difference was observed between the two groups at any hours of the study, however (Table 1). None of the patients experienced any side effects, including nausea, vomiting, sedation, and burning sensation.

5. Discussion

Results of the current study demonstrated that the addition of magnesium sulfate to ropivacaine, in TAP block after hysterectomy, had no effect on the pain score and on the amount of rescue analgesic consumption. By blocking the T6-L1 nerve roots, TAP block provides effective analgesia for the abdominal wall (21). The exact location of the needle for injection is the fascial layer between the internal oblique and the transverse abdominis muscles, which is the major pathway of the abdominal wall nerves (22, 23).

According to usefulness of the TAP block in postoperative pain management, efforts are made to improve its effect in recent years. One of the medicines to enhance the effect of local anesthetic is magnesium sulfate. Regulation of

Table 1. Patients' Characteristics, VAS Pain Score, and Number of Rescue Analgesic Consumption in the Study Groups[a]

Assessment Item	Group R	Group RM	P Value
Patients' characteristics			
Age, y	40.7 ± 11	40.4 ± 12	0.924
Weight, kg	62.9 ± 11	63.6 ± 6	0.774
Pain Score, h			
1st	5.7 ± 0.9	5.9 ± 1.1	0.549
2nd	2.9 ± 0.5	2.7 ± 0.4	0.299
6th	3 ± 0.6	2.7 ± 0.7	0.09
12th	3.5 ± 1.04	3.4 ± 0.7	0.779
24th	3.1 ± 0.7	2.8 ± 0.7	0.244
Number of rescue analgesic consumption, h			
1st	1 (1.7)	2 (3.3)	0.561
2nd	3 (5)	0 (0)	0.078
6th	6 (10)	3 (5)	0.286
12th	14 (23.3)	15 (25)	0.800
24th	4 (6.7)	8 (13.3)	0.203
Total	28 (46.6)	28 (46.6)	0.580

[a]Values are presented as mean ± SD or No. (%).

calcium influx into the cell and antagonism of N-methyl-D-aspartate (NMDA) receptors in the central nervous system are introduced as the two mechanisms, which underlie its analgesic properties (24).

In a systematic review performed on nine studies to assess the efficacy of TAP block in decreasing opioid consumption and postoperative pain scores in caesarean delivery, its effectiveness was observed in all the studies. The only group that had better analgesia than the TAP block groups was the one that received intrathecal morphine, at the expense of an increased incidence of side effects (21). However, considering the quality of pain in patients undergoing caesarean section, which is a mixed somatic and visceral pain, better pain management with intrathecal morphine is warranted. TAP analgesia blocks only somatic pain. However, the current study was strongly influenced by the heterogeneity of the studies with regards to the dosage of drug, the quality of block, and the way of performance.

In another systematic review conducted on 34 studies, the superiority of this type of block over other postoperative pain management techniques was demonstrated. However, further studies were strongly recommended by the researchers on how the block is performed, the dosage of medications administered, and the use of adjuvant drugs in various surgical procedures (25). The beneficial effects of the transverse abdominis plane block are confirmed in many studies so far (8-13, 15-18). However, its duration of effect is challenging.

In a study on pharmacokinetics of the local anesthetic drug, the prolonged duration of analgesic effect of the block (36 - 48 hours), due to slow drug clearance, and minimal adverse effects of systemic absorption of the drug, owing to the relatively poor vascularization of the block site, was noted (26). Nevertheless, the clinical effectiveness of medications is far less than this amount.

In some studies, a number of questions are raised as to the precise time of block administration and finding methods to prolong the effect of the block (27).

In a study, TAP catheters were placed for 36 hours after abdominal surgery. In addition to the technical issues of TAP catheter insertion using the posterior approach, the small number of patients was of the main constraints of the study (16).

In another study, in comparison with lateral approach in TAP block, benefits of posterior approach were demonstrated (28).

The effect of local anesthetic infusion on the abdominal wall is investigated in connection with analgesia induction in healthy people and with postoperative pain management in cesarean section and inguinal hernia repair, which produced different results (29-32). Thus, employing other techniques, rather than catheterization, seems necessary to prolong the duration of the effect of TAP block.

In a meta-analysis to evaluate the analgesic effect of systemic magnesium sulfate on postoperative pain, reduction of opioid consumption in all groups receiving magnesium sulfate and reduction of pain score on the first day after surgery were observed, without any side effects. There was no difference between the two modes of magnesium sulfate administration; bolus or continuous infusion (24).

The synergistic effect of magnesium sulfate with intrathecal bupivacaine and lidocaine is investigated for postoperative pain and shivering (20, 33).

Moreover, addition of magnesium sulfate to lidocaine as continuous infusion in the axillary block reduced pain and opioid consumption (34).

In a comprehensive study, the researchers studied the different techniques of TAP block administration in various surgery procedures. By examining several existing studies in gynecological surgeries, Chin et al. considered the effect of TAP block only limited to the early time after surgery, due to its major effect on the somatic pain than on the visceral pain. Regarding pharmacological considerations, they found the addition of mexamethasone and dexmedetomidine to the local anesthetic mixture somewhat promising, but the addition of clonidine to the local anesthetic was ineffective (35).

In another study conducted by Rana et al. a bilateral TAP block was performed on patients undergoing abdominal hysterectomy under intrathecal anesthesia, with 18 mL bupivacaine 0.25% alone or in combination with 150 mg magnesium sulfate. Reduced pain score and rescue analgesic consumption as well as increased duration of analgesia were the outcome (36).

According to the pain score and rescue analgesic consumption, the result of the current study was not in agreement with those of Rana et al. The difference, both in the applied anesthesia techniques (general vs. intrathecal) for the surgery and in the types of the administered analgesics in the TAP block (bupivacaine vs. ropivacaine) between the two studies might explain the incongruity. In the current study, the two types of pain were measured both at rest and during movement, while in theirs the type of pain was not mentioned. In terms of technique, the location of needle insertion in the current study was close to the mid axillary line while it was in the anterior axillary line in their study.

Although in the current study the addition of auxiliary magnesium sulfate to ropivacaine did not exhibit any increased analgesic effect, it is recommended that further studies be conducted with different doses of the drug and with other auxiliary drugs as well.

Footnote

Conflict of Interests: Authors declare that they have no conflict of interest regarding this study.

References

1. Farzi F, Naderi Nabi B, Mirmansouri A, Fakoor F, Atrkar Roshan Z, Biazar G, et al. Postoperative pain after abdominal hysterectomy: a randomized, double-blind, controlled trial comparing the effects of tramadol and gabapentin as premedication. *Anesth Pain Med*. 2016;**6**(1). e32360. doi: 10.5812/aapm.32360.
2. Imani F, Rahimzadeh P. Gabapentinoids: gabapentin and pregabalin for postoperative pain management. *Anesth Pain Med*. 2012;**2**(2):52–3. doi: 10.5812/aapm.7743. [PubMed: 24223337]. [PubMed Central: PMC3821114].
3. Imani F. Postoperative pain management. *Anesth Pain Med*. 2011;**1**(1):6–7. doi: 10.5812/aapm.1810.
4. Imani F, Faiz HR, Sedaghat M, Hajiashrafi M. Effects of adding ketamine to fentanyl plus acetaminophen on postoperative pain by patient controlled analgesia in abdominal surgery. *Anesth Pain Med*. 2014;**4**. e12162.
5. Vadivelu N, Mitra S, Narayan D. Recent advances in postoperative pain management. *Yale J Biol Med*. 2010;**83**(1):11–25. [PubMed: 20351978]. [PubMed Central: PMC2844689].
6. Gupta A, Kaur K, Sharma S, Goyal S, Arora S, Murthy RS. Clinical aspects of acute post-operative pain management & its assessment. *J Adv Pharm Technol Res*. 2010;**1**:97–108.
7. Taylor R, Pergolizzi JV, Sinclair A, Raffa RB, Aldington D, Plavin S, et al. Transversus abdominis block: clinical uses, side effects, and future perspectives. *Pain Pract*. 2013;**13**(4):332–44. doi: 10.1111/j.1533-2500.2012.00595.x.
8. Ra YS, Kim CH, Lee GY, Han JL. The analgesic effect of the ultrasound-guided transverse abdominis plane block after laparoscopic cholecystectomy. *Korean J Anesthesiol*. 2010;**58**(4):362. doi: 10.4097/kjae.2010.58.4.362.
9. Torup H, Bogeskov M, Hansen EG, Palle C, Rosenberg J, Mitchell AU, et al. Transversus abdominis plane (TAP) block after robot-assisted laparoscopic hysterectomy: a randomised clinical trial. *Acta Anaesthesiol Scand*. 2015;**59**(7):928–35. doi: 10.1111/aas.12516. [PubMed: 26032118].
10. Onishi Y, Kato R, Okutomi T, Tabata K, Amano K, Unno N. Transversus abdominis plane block provides postoperative analgesic effects after cesarean section: Additional analgesia to epidural morphine alone. *J Obstet Gynaecol Res*. 2013;**39**(9):1397–405. doi: 10.1111/jog.12074.
11. Telnes A, Skogvoll E, LonnEE H. Transversus abdominis plane block vs. wound infiltration in Caesarean section: a randomised controlled trial. *Acta Anaesthesiol Scand*. 2015;**59**(4):496–504. doi: 10.1111/aas.12498.
12. Suresh S, Taylor LJ, De Oliveira GS, Lonnqvist PA. Dose effect of local anesthetics on analgesic outcomes for the transversus abdominis plane (TAP) block in children: a randomized, double-blinded, clinical trial. *Paediatr Anaesth*. 2015;**25**(5):506–10. doi: 10.1111/pan.12550.
13. Pather S, Loadsman JA, Gopalan PD, Rao A, Philp S, Carter J. The role of transversus abdominis plane blocks in women undergoing total laparoscopic hysterectomy: a retrospective review. *Aust N Z J Obstet Gynaecol*. 2011;**51**(6):544–7. doi: 10.1111/j.1479-828X.2011.01369.x. [PubMed: 21923857].
14. Gharaei H, Imani F, Almasi F, Solimani M. The effect of ultrasound-guided TAPB on pain management after total abdominal hysterectomy. *Korean J Pain*. 2013;**26**(4):374–8. doi: 10.3344/kjp.2013.26.4.374.
15. Lee AR, Choe YS. Anesthesia experience for open gastrostomy with ultrasound-guided unilateral subcostal transversus abdominis plane block in a high risk elderly patient: a case report. *Anesth Pain Med*. 2015;**5**(3). e24890. doi: 10.5812/aapm.24890v2.
16. Bjerregaard N, Nikolajsen L, Bendtsen TF, Rasmussen BS. Transversus abdominis plane catheter bolus analgesia after major abdominal surgery. *Anesthesiol Res Pract*. 2012;**2012**:1–5. doi: 10.1155/2012/596536.
17. Kartalov A, Jankulovski N, Kuzmanovska B, Zdravkovska M, Shosholcheva M, Spirovska T, et al. Effect of adding dexamethasone as a ropivacaine adjuvant in ultrasound-guided transversus abdominis plane block for inguinal hernia repair. *Pril (Makedon Akad Nauk Umet Odd Med Nauki)*. 2015;**36**(3):35–41. doi: 10.1515/prilozi-2015-0076.
18. Niraj G, Kelkar A, Hart E, Horst C, Malik D, Yeow C, et al. Comparison of analgesic efficacy of four-quadrant transversus abdominis plane (TAP) block and continuous posterior TAP analgesia with epidural analgesia in patients undergoing laparoscopic colorectal surgery: an open-label, randomised, non-inferiority trial. *Anaesthesia*. 2014;**69**(4):348–55. doi: 10.1111/anae.12546.
19. Dabbagh A, Elyasi H, Razavi SS, Fathi M, Rajaei S. Intravenous magnesium sulfate for post-operative pain in patients undergoing lower limb orthopedic surgery. *Acta Anaesthesiol Scand*. 2009;**53**(8):1088–91. doi: 10.1111/j.1399-6576.2009.02025.x.
20. Xiao F, Xu W, Feng Y, Fu F, Zhang X, Zhang Y, et al. Intrathecal magnesium sulfate does not reduce the ED50 of intrathecal hyperbaric bupivacaine for cesarean delivery in healthy parturients: a prospective, double blinded, randomized dose-response trial using the sequential allocation method. *BMC Anesthesiol*. 2017;**17**(1):8. doi: 10.1186/s12871-017-0300-z.
21. Mishriky BM, George RB, Habib AS. Transversus abdominis plane block for analgesia after Cesarean delivery: a systematic review and meta-analysis. *Can J Anaesth*. 2012;**59**(8):766–78. doi: 10.1007/s12630-012-9729-1.
22. Mukhtar K. Transversus abdominis plane (TAP) block. *JNY School Reg Anesth*. 2009;**12**:28–33.
23. Kiefer N, Krahe S, Gembruch U, Weber S. Ultrasound anatomy of the transversus abdominis plane region in pregnant women before and after cesarean delivery. *BMC Anesthesiol*. 2016;**16**(1):126. doi:

10.1186/s12871-016-0289-8. [PubMed: 28007030]. [PubMed Central: PMC5180404].
24. Albrecht E, Kirkham KR, Liu SS, Brull R. Peri-operative intravenous administration of magnesium sulphate and postoperative pain: a meta-analysis. *Anaesthesia*. 2013;**68**(1):79–90. doi: 10.1111/j.1365-2044.2012.07335.x. [PubMed: 23121612].
25. Young MJ, Gorlin AW, Modest VE, Quraishi SA. Clinical implications of the transversus abdominis plane block in adults. *Anesthesiol Res Pract*. 2012;**2012**:731645.
26. McDonnell JG, Curley G, Carney J, Benton A, Costello J, Maharaj CH, et al. The analgesic efficacy of transversus abdominis plane block after cesarean delivery: a randomized controlled trial. *Anesth Analg*. 2008;**106**(1):186–91. doi: 10.1213/01.ane.0000290294.64090.f3.
27. Shin HJ, Kim ST, Yim KH, Lee HS, Sim JH, Shin YD. Preemptive analgesic efficacy of ultrasound-guided transversus abdominis plane block in patients undergoing gynecologic surgery via a transverse lower abdominal skin incision. *Korean J Anesthesiol*. 2011;**61**(5):413–8. doi: 10.4097/kjae.2011.61.5.413.
28. Faiz SHR, Alebouyeh MR, Derakhshan P, Imani F, Rahimzadeh P, Ghaderi Ashtiani M. Comparison of ultrasound-guided posterior transversus abdominis plane block and lateral transversus abdominis plane block for postoperative pain management in patients undergoing cesarean section: a randomized double-blind clinical trial study. *J Pain Res*. 2018;**11**:5–9. doi: 10.2147/JPR.S146970. [PubMed: 29296094]. [PubMed Central: PMC5741073].
29. Petersen PL, Hilsted KL, Dahl JB, Mathiesen O. Bilateral transversus abdominis plane (TAP) block with 24 hours ropivacaine infusion via TAP catheters: A randomized trial in healthy volunteers. *BMC Anesthesiol*. 2013;**13**(1):30. doi: 10.1186/1471-2253-13-30.
30. Le-Wendling L, Ihnatsenka B, Haller A, Esch AT, Boezaart AP. The insiders' experiences with continuous transversus abdominis plane blocks for analgesia after cesarean delivery. *Pain Med*. 2013;**14**(2):305–8. doi: 10.1111/j.1526-4637.2012.01341.x.
31. Heil JW, Nakanote KA, Madison SJ, Loland VJ, Mariano ER, Sandhu NS, et al. Continuous transversus abdominis plane (TAP) blocks for postoperative pain control after hernia surgery: a randomized, triple-masked, placebo-controlled study. *Pain Med*. 2014;**15**(11):1957–64. doi: 10.1111/pme.12530.
32. Kim MG, Kim SI, Ok SY, Kim SH, Lee SJ, Park SY, et al. The analgesic effect of ultrasound-guided transverse abdominis plane block after laparoscopic totally extraperitoneal hernia repair. *Korean J Anesthesiol*. 2012;**63**(3):227–32. doi: 10.4097/kjae.2012.63.3.227. [PubMed: 23060979]. [PubMed Central: PMC3460151].
33. Faiz SHR, Rahimzadeh P, Imani F, Bakhtiari A. Intrathecal injection of magnesium sulfate: shivering prevention during cesarean section: a randomized, double-blinded, controlled study. *Korean J Anesthesiol*. 2013;**65**(4):293. doi: 10.4097/kjae.2013.65.4.293.
34. Haghighi M, Soleymanha M, Sedighinejad A, Mirbolook A, Naderi Nabi B, Rahmati M, et al. The effect of magnesium sulfate on motor and sensory axillary plexus blockade. *Anesth Pain Med*. 2015;**5**(1). e21943. doi: 10.5812/aapm.21943.
35. Chin KJ, McDonnell JG, Carvalho B, Sharkey A, Pawa A, Gadsden J. Essentials of our current understanding. *Regional Anesth Pain Med*. 2017;**42**(2):133–83. doi: 10.1097/aap.0000000000000545.
36. Rana S, Verma RK, Singh J, Chaudhary SK, Chandel A. Magnesium sulphate as an adjuvant to bupivacaine in ultrasound-guided transversus abdominis plane block in patients scheduled for total abdominal hysterectomy under subarachnoid block. *Indian J Anaesth*. 2016;**60**(3):174–9. doi: 10.4103/0019-5049.177879. [PubMed: 27053780]. [PubMed Central: PMC4800933].