Original Research Article

Evaluation of Controlled HypotensiveAnesthesia in spine surgeriesby Comparative Administration of Dexmedetomidine and Nitroglycerine

Vinay Kumar*

Senior Resident, Department of Anaesthesia,Vardhman Institute of Medical Science, Pawapuri, Nalanda, Bihar, India

Received: 20-05-2020 / Revised: 30-06-2020 / Accepted: 10-07-2020

Abstract

Controlled hypotension or induced hypotension is a technique to reduce the blood loss and the necessity of blood transfusion during surgery by improving the visibility of the surgical site and decreasing the arterial blood pressure until hypotension is reached. Hence based on above findings the present study was planned for Evaluation of Controlled Hypotensive Anesthesia in spine surgeries by Comparative Administration of Dexmedetomidine and Nitroglycerine.The present study was planned in Department of Anaesthesia, Vardhman Institute of Medical Science Pawapuri. Nalanda, Bihar. The study was conducted from November 2015 to December 2016. In the present study total 40 patients were selected undergoing the spine surgeries were evaluated. The cases were divided in two study groups as Group D and Group N. The study drug dexmeditomidine was given to group D in the dose of 1 micro gram/kg body weight in a 600 seconds infusion before induction diluted to 10 ml with normal saline followed by maintenance dose at infusion rate of 0.2 - 0.7 microgm/kg. The group N received 10 ml plain normal saline over 600 seconds before induction The data generated from the present study concludes that Controlled hypotension using dexmeditomidine as bolus dose 1 microgram per kg intravenous over 10 minutes prior to induction followed by continuous intravenous infusion at 0.2 - 0.7 microgram per kg per hour, provided more stable hemodynamics and better surgical field quality compared to nitroglycerine intraoperative infusion at 0.5 to 10 microgram/kg/min.

Keywords: Controlled Hypotensive Anesthesia, Dexmedetomidine, Nitroglycerine, spine surgeries, etc.

Introduction

In recent decades, increased understanding of spinal biomechanics, proliferation of sophisticated spinal instrumentation devices, advances in bone fusion techniques, refinement of anterior approaches to the spine, and development of microsurgical and minimally invasive methods have made it possible to stabilize every segment of the spine successfully, regardless of the offending pathology. Accordingly, use of spinal fusion and instrumentation has increased. The question facing the modern spine surgeon is not so much how to stabilize the spine but when to do so.

**Correspondence*
Dr.Vinay Kumar
Senior Resident, Department of Anaesthesia, Vardhman Institute of Medical Science, Pawapuri, Nalanda, Bihar, India.

As defined by White and Panjabi, [1] spinal stability is the ability of the spine under physiologic loads to limit patterns of displacement so as not to damage or irritate the spinal cord and nerve roots and, in addition, so as to prevent incapacitating deformity or pain due to structural changes; instability (acute or chronic) refers to excessive displacement of the spine that would result in neurologic deficit, deformity, or pain.

It should be noted that whereas the term fusion, as used in this article and in spine literature to refer to the concept of internal stabilization of the spine, generally refers to fusion with instrumentation (instrumented fusion), such stabilization has also, albeit with decreasing frequency, been accomplished by means of bone grafting alone.

A great deal of controversy remains regarding the application of fusion surgery in the treatment of

degenerative spine disease without overt instability. In the future, these controversies will be addressed by a two-pronged approach. First, rigorous randomized controlled trials are needed to better assess the efficacy of existing methods of fusion. Second, novel treatment strategies are needed to replace fusion surgery.

Disk arthroplasty and posterior dynamic stabilization devices are two strategies that are under investigation. Some brands of artificial disk (see the image below) for treatment of symptomatic lumbar degenerative disk disease have been approved by the US Food and Drug Administration (FDA). Short-term studies revealed equivalent results for disk arthroplasty and lumbar fusion. [2]

A prospective, randomized, controlled multicenter study designed to show the "noninferiority" of cervical total disk replacement (TDR) revealed that this technology was at least equivalent to anterior cervical diskectomy and fusion with regard to outcome at 24 months. [3] Although most primary outcome measures (eg, pain scores and neurologic success) were equivalent in the two groups, the disk replacement group showed a lower requirement for analgesics and lower reoperation rate than the fusion group at 24 months.

Although these results show promise for total disk replacement, it should be noted that this study was limited to patients with single-level disk disease with radiculopathy and and that the results therefore cannot be generalized to patients with multilevel disk herniations, spondylosis, spondylolisthesis, and degenerative disk disease. In addition, long-term follow-up studies are needed to determine whether these benefits last, whether motion preservation with artificial disks persists over the long term, and whether the frequency of transition-level syndrome is decreased.

Posterior dynamic stabilization devices come in several varieties. The most promising of these are pedicle screw-based systems, where the screws are linked by flexible members instead of rigid rods. The theoretical goal is to limit movement to a zone where neutral or near-neutral loading of spine occurs, or conversely prevent movement into a zone where abnormal loading occurs. Again, the clinical trials that have been conducted to date have produced clinical outcomes comparable with fusion. [4]

The challenges facing artificial disks and posterior dynamic stabilization devices are twofold. First, they must improve upon lumbar fusion outcomes. Second, these mechanical devices must continue to function indefinitely, as opposed to current spine implants, which are shielded from biomechanical stress once bony fusion is achieved.

In the long-term future, biologic rather than mechanical treatment strategies directed at repairing and maintaining the degenerated spine elements are more likely to provide a satisfactory solution to the problem of degenerative spine disease.Regional variations in vertebral anatomy affect the incidence and consequences of spinal instability in different parts of the spine and dictate the surgical means by which the spine can be stabilized.

Vertebral body size increases as one descends the spine, accompanied by a corresponding increase in vertebral axial load-bearing capacity. The greater cancellous-to-cortical bone ratio in the vertebral body as compared with the posterior vertebral elements makes the body more susceptible to neoplastic and infectious diseases, and its relation to the instantaneous axis of rotation (IAR) makes it more susceptible to compressive injuries. The relative preponderance of these disorders anterior to the spinal cord makes their surgical management more challenging, often necessitating an anterior surgical approach to the spine.

On the other hand, the large surface area and volume of the vertebral body make it an excellent target for insertion of screw/plate systems, which can be used to stabilize every segment of the subaxial spine.

Facet joints have a transverse orientation in the cervical spine and gradually acquire a more sagittal orientation throughout the thoracic and upper lumbar spine. They then become more coronally oriented as one descends the lumbar spine. The transverse orientation of the facet joints and the loose facet capsules in the cervical spine allow relatively free movement of the neck in all three planes and do not protect the cervical spine against flexion injuries.

In the thoracolumbar junction, the sagittal orientation of the facet joints and the strong capsular ligaments permit greater movement in the sagittal plane than in other directions. This facet orientation and the transitional location of the thoracolumbar spine between the ribcage-stabilized thoracic spine and the more robust lumbar spine make the thoracolumbar junction more susceptible to flexion injuries.

The more coronal orientation of the L5-S1 facet joints as compared with the L4-5 facets accounts for the lower incidence of degenerative spondylolisthesis at L5-S1, in spite of the biomechanically disadvantaged angle of the lumbosacral junction. In contrast, isthmic spondylolisthesis, where the presence of spondylolysis bypasses the resistance of facet joints against translation, is more frequent at L5-S1.

The spinal canal is narrowest in the thoracic spine. On the other hand, the thoracic spine is stabilized by the ribcage, making it relatively immune to degenerative instability and increasing its resistance to traumatic instability. Consequently, if the force vector is great enough to overcome the stability of thoracic spine and produce a fracture-dislocation, the likelihood and severity of spinal cord injury would be greater in this area than elsewhere in the spine.

The pedicles in the cervical spine are quite narrow, short, acutely oriented, and juxtaposed to the transverse foramina (of the vertebral artery); accordingly, they are relatively undesirable for screw insertion. In contrast, the large size, strength, and favorable cylindrical anatomy of the pedicles in the lumbar spine makes them ideal for screw insertion. The pedicle screws at different segments are then linked by rods to stabilize the spine.

The pedicles acquire a relatively sagittal orientation in the thoracic and upper lumbar spine but then point inward again as one approaches the sacrum, a fact that must be taken into account when pedicle screws are to be inserted. In the thoracic spine, the pedicles have a narrow transverse diameter, exhibit a slight downward angle, and are located next to the narrow thoracic spinal canal.

Because of these anatomic considerations, wires and hooks have been used more frequently than screws to anchor rods against the thoracic spine, necessitating long instrumentation constructs to stabilize a short segment of instability ("rod long, fuse short"). Increasingly, screws are used in the thoracic spine to create shorter and stronger instrumentation constructs. In this setting, it is imperative to select screws of appropriate diameter on the basis of preoperative computed tomography (CT) and to avoid breach of the medial pedicle wall, erring toward the laterally located and protective costovertebral articulation, if necessary.

On the other hand, the relatively generous sagittal diameter of thoracic pedicles and the smaller size and lesser functional importance of thoracic nerve roots make screw misdirection in the sagittal plane less costly in the thoracic spine than it would be in the lumbar spine.

Cervical vertebrae have anatomic structures not found elsewhere in the spine: the lateral masses. Juxtaposed between the pedicles and the lamina and delimited by the articular surfaces of the adjacent facet joints, the paired lateral masses are satisfactory targets for screw insertion. Lateral mass screws at adjacent segments are linked by plates or rods to stabilize the cervical spine.

Laminae, spinous processes, and transverse processes can be used as anchor points for wires and hooks connected to rods to form three-point-bending instrumentation constructs. Alternatively, these structures can be wired to each other at different segments to produce tension band constructs. In general, these types of constructs provide less stiffness than screw/rod or screw/plate systems.

Controlled hypotension or induced hypotension is a technique to reduce the blood loss and the necessity of blood transfusion during surgery by improving the visibility of the surgical site and decreasing the arterial blood pressure until hypotension is reached. Hence based on above findings the present study was planned for Evaluation of Controlled Hypotensive Anesthesia in spine surgeries by Comparative Administration of Dexmedetomidine and Nitroglycerine.

Methodology

The present study was planned in Department of Anaesthesia, Vardhman Institute of Medical Science Pawapuri. Nalanda, Bihar. The study was conducted from November 2015 to December 2016.In the present study total 40 patients were selected undergoing the spine surgeries were evaluated. The cases were divided in two study groups as Group D and Group N. The study drug dexmeditomidine was given to group D in the dose of 1 micro gram/kg body weight in a 600 seconds infusion before induction diluted to 10 ml with normal saline followed by maintenance dose at infusion rate of 0.2 - 0.7 microgm/kg. The group N received 10 ml plain normal saline over 600 seconds before induction followed by maintenance dose of nitroglycerine at an infusion rate of 0.5 - 10 microgm/kg/min.

The 50 ml syringe were labelled as LD and MD for laoding dose and maintenanace dose respectively. For patients in group D X, LD syringe contained the bolus dose of dexmedetomidine at 1 microgm /kg diluted to

10 ml with required amount of normal saline and MD had 2 microgm /kg prepared by taking 1 ml (100 microgm) of inj. dexmeditomidine diluted with 49 ml of normal saline. For group N G patients, LD syringe had 10 ml of plain normal saline and MD had 100 microgm/ml of nitroglycerin prepared by taking 1 ml (5 mg) of nitroglycerin diluted with 49 ml of normal saline. The anaesthesiologist responsible for providing anaesthesia and observing the parameters during the surgery and the patient were kept unaware of the content of the syringes. After arrival in the preanaesthesia room 20 G and 18 Gintravenous cannula were inserted at different anatomical sites for the infusion of the study drug and for the administration of fluids and other drug/ blood respectively.

All the patients were informed consents. The aim and the objective of the present study were conveyed to them. Approval of the institutional ethical committee was taken prior to conduct of this study.

Following was the inclusion and exclusion criteria for the present study.

Inclusion Criteria: Cases belonging to ASA class I or II between 18 and 60 years of age scheduled for elective spine surgeries.

Exclusion criteria: Cases of ASA grade III, IV, uncontrolled diabetes mellitus, pulmonary disease, uncontrolled hypertension, ischemic heart disease, gastro-esophageal reflux disease, cerebral ischemia and renal impairment. History of difficult airway management. Body mass index >40, history of neuromuscular disease, pregnancy. • Known allergy to all study drugs. Prior treatment with calcium channel blockers, opioids, anticoagulants and patients receiving magnesium supplementation or drugs known to have a significant interaction with NMDAs.

Results and Discussion

Controlled hypotension involves reducing arterial blood pressure 30-40% below its normal range or reducing mean arterial pressure (MAP) to 65 mmHg reversibly and maintaining it at that level throughout the surgery. [5] A variety of medications can be used to induce intra-operative hypotension including vasodilators like sodium nitroprusside, [6] nitroglycerin [7] and hydralazine; inhaled anesthetics like isoflurane [8] and sevoflurane; intravenous anesthetics like propofol; beta adrenergic antagonists like esmolol; [9] trimethaphan, adenosine and α2 agonists. Some of the reported disadvantages with the use of these agents include resistance to vasodilators, tachyphylaxis with nitroglycerin, cyanide toxicity with the use of nitroprusside and delayed recovery from anesthesia with the use of high doses of inhaled anesthetics. [10]

An important technique to reduce bleeding during the surgery is controlled reduction in blood pressure to such levels so that bleeding is minimal, but at the same time perfusion to the vital organs is well-maintained. This is the underlying concept for controlled hypotensive anesthesia. [11] Reduced bleeding in the operative site improves the quality of the surgical field, decreases the number of manipulations as well as the incidence of major complications and shortens the surgical time. [12]

Dexmedetomidine, a selective α2 adrenoceptor agonist, causes reduction in blood pressure, slowing of HR, sedation and analgesia. The fall in blood pressure is mainly due to inhibition of central sympathetic outflow and also due to stimulation of presynaptic α2 adrenoceptors decreasing norepinephrine release. [13] An important advantage is its minimal respiratory depressant effect with potent sedative and analgesic effects compared with opioids and other sedatives. A few studies have shown that dexmedetomidine decreases the bleeding in surgeries within the framework of hemodynamic stability. [14]

Table 1: Basic Details

Group	**Group D**	**Group N**
Administration of	Dexmeditomidine	Nitroglycerine
Group of	Cases	Control
No. of Cases	20	20
Age (years)	29 – 46	31 - 45
Sex: Males Females	 12 8	 15 5
Weight (kg)	51.2 – 63.8	54.1 – 72.3
BMI (kg/m^2)	20.5 – 24.7	21.1 – 24.9
Baseline Hear Rate	85 – 104	79 – 109
Mean arterial pressure (mm hg)	93.4 – 101.5	90.4 – 102.3
Duration of Surgery (min)	70.1 – 85.9	69.5 – 91.3

Table 2: Fromme Boezaart surgical field grade

Group	**Group D**			**Group N**		
Administration of	Dexmeditomidine			Nitroglycerine		
Group of	Cases			Control		
No. of Cases	20			20		
	15 min	30 min	45 min	15 min	30 min	45 min
Grade 0	0	0	0	0	0	0
Grade 1	0	2	1	0	0	0
Grade 2	16	17	18	8	10	14
Grade 3	4	1	2	12	10	6
Grade 4	0	0	0	0	0	0
Grade 5	0	0	0	0	0	0

Table 3: Heart Rate changes

Group	**Group D**	**Group N**
Administration of	Dexmeditomidine	Nitroglycerine
Group of	Cases	Control
No. of Cases	20	20
Heart Rate bpm		
Baseline	85 – 103	79 – 102
Start of surgery	65 – 84	88 – 122
End of surgery	63 – 66	78 – 106
15 mins post extubation	71 – 78	96 - 110

Table 4: Mean arterial pressure

Group	**Group D**	**Group N**
Administration of	Dexmeditomidine	Nitroglycerine
Group of	Cases	Control
No. of Cases	20	20
Mean arterial pressure mm hg		
Baseline	93 – 102	90 – 102
Start of surgery	70 – 74	86 – 95
End of surgery	68 – 74	69 – 78
15 mins post extubation	76 – 80	88 - 101

Jamaliya et al. [15] found that continuous infusion of dexmedetomidine is effective in minimizing blood loss and maintaining superior haemodynamics as compared with nitroglycerine in posterior fixation spine surgery. Nasreen et al. [16] in study assessing the hypotensive effect of dexmedetomidine administered s a 0.4 µg/kg/h IV infusion following a 1 µg/kg IV bolus dose in middle ear surgery, it has been reported that surgeon satisfaction was increased and inhalation agent necessity to decrease the mean arterial pressure up to 30% was decreased in dexmedetomidine administered patient group. Secondary decrease in the heart rate and blood pressure caused by dexmedetomidine is considered to be responsible for this situation.

In study conducted by Vali et al. [17] comparing dexmedetomidine with nitroglycerine in patients undergoing posterior fixation surgery after traumatic spine fractures dexmedetomidine had better control over vital parameters e.g heart rate, mean arterial pressure, systolic blood pressure and diastolic blood pressure than nitroglycerine. In study conducted by Rokhtabnak et al. [17] compring dexmedetomidine with magnesium sulfate, blood pressure control was easier in the dexmedetomidine group that`s number of patients that required nitroglyerine or analgesic rescue administration was lower in dexmedetomidine group. As regard duration of surgery there was stastically significant difference with duration of surgery shorter in dexmedetomidine group followed by magnesium sulfate group then nitroglycerine group. These results suggest that dexmedetomidine is the best regard visual field and duration of surgery.

With agreement to these results, study conducted by Vali et al. [17] to compare dexmedetomidine and

nitroglycerine in posterior fixation surgery following traumatic spine surgery showed that surgeries in nitroglycerine group lasted for longer duration than dexmedetomidine group with difference being stastically significant

The Khalifa et al. [19] also observed no significant difference in amount of blood loss in dexmedetomidine group, nitroglycerine group as well as magnesium sulphate group. Our results were in contrast with the result of Jamaliya et al. [20]. Hey observed that amount of blood loss and blood transfusion requirement were significantly higher in NTG group than in DEX group. Actually they carried out this study in spine surgeries and blood loss in spine surgery is mainly dependent on congestion of veins around the vertebral bodies. NTG is a peripheral vasodilator agent with its predominant select on veins. Dilatation of the venous plexus around the vertebral bodies may have contributed to increased blood loss when NTG was used for controlled hypotension. Durmus et al. [21] have proved in a placebo controlled study that dexmedetomidine decreased bleeding in patients undergoing tympanoplasty and septorhinoplasty.

Many anesthetic agents and vasoactive drugs are used frequently to produce controlled hypotension, including inhalational anesthetics, direct-acting vasodilators, autonomic ganglion blockers, β-adrenergic blockers, and calcium channel blockers. It was in 1985 M Guggiari et al., used nitroglycerine (NTG) [22] for the first time to produce induced hypotension in aneurismal brain surgery and proved that it can be used as a sole agent for hypotension. The decrease in arterial pressure is achieved by vasodilatory effect of NTG on arterial and venous bed resulting finally in decreased venous and right heart filling and so decreased cardiac output.Nitroglycerine causes either no change or slight tachycardia during continuous infusion as slight increase in heart rate is reflex phenomenon, baroreceptor response secondary to hypotension produced.

An important technique to reduce bleeding during the surgery is controlled reduction in blood pressure to such levels so that bleeding is minimal, but at the same time perfusion to the vital organs is well-maintained. This is the underlying concept for controlled hypotensive anesthesia. [23] Reduced bleeding in the operative site improves the quality of the surgical field, decreases the number of manipulations as well as the incidence of major complications and shortens the surgical time. [24]

Conclusion

The data generated from the present study concludes that Controlled hypotension using dexmeditomidine as bolus dose 1 microgram per kg intravenous over 10 minutes prior to induction followed by continuous intravenous infusion at 0.2 - 0.7 microgram per kg per hour, provided more stable hemodynamics and better surgical field quality compared to nitroglycerine intraoperative infusion at 0.5 to 10 microgram/kg/min.

References

1. White AA, Panjabi MM. Clinical Biomechanics of the Spine. 2nd ed. Philadelphia: Lippincott; 1990. 30-342.
2. Lin EL, Wang JC. Total disk arthroplasty. J Am Acad Orthop Surg. 2006 ;14 (13):705-14.
3. Murrey D, Janssen M, Delamarter R, Goldstein J, Zigler J, Tay B, et al., Results of the prospective, randomized, controlled multicenter Food and Drug Administration investigational device exemption study of the ProDisc-C total disc replacement versus anterior discectomy and fusion for the treatment of 1-level symptomatic cervical disc disease. Spine J. 2009;9 (4):275-86.
4. Schwarzenbach O, Berlemann U, Stoll TM, Dubois G. Posterior dynamic stabilization systems: DYNESYS. Orthop Clin North Am. 2005;36 (3):363-72.
5. Van Aken H, Miller D. Delibrate hypotension. In: Miller RD, editor. Anesthesia. New York, USA: Churchill Livingstone Inc.; 2000. p. 1470-90.
6. Degoute CS, Ray MJ, Manchon M, Dubreuil C, Banssillon V. Remifentanil and controlled hypotension; comparison with nitroprusside or esmolol during tympanoplasty. Can J Anaesth 2001;48:20-7.
7. Srivastava U, Dupargude AB, Kumar D, Joshi K, Gupta A. Controlled hypotension for functional endoscopic sinus surgery: Comparison of esmolol and nitroglycerine. Indian J Otolaryngol Head Neck Surg 2013;65:440-4.
8. Mandal P. Isoflurane anaesthesia for functional endoscopis sinus surgery. Indian J. Anaesth 2003;47:37-40.
9. Degoute CS. Controlled hypotension: A guide to drug choice. Drugs 2007;67:1053-76.
10. Shams T, El Bahnasawe NS, Abu-Samra M, El-Masry R. Induced hypotension for functional endoscopic sinus surgery: A comparative study of dexmedetomidine versus esmolol. Saudi J Anaesth 2013;7:175-80.

11. Tobias JD. Controlled hypotension in children: A critical review of available agents. Paediatr Drugs 2002;4:439-53.
12. Baker AR, Baker AB. Anaesthesia for endoscopic sinus surgery. Acta Anaesthesiol Scand 2010;54:795-803.
13. Hall JE, Uhrich TD, Barney JA, Arain SR, Ebert TJ. Sedative, amnestic, and analgesic properties of small-dose dexmedetomidine infusions. Anesth Analg 2000;90:699-705.
14. Kol IO, Kaygusuz K, Yildirim A, Dogan M, Gursoy S, Yucel E, et al. Controlled hypotension with desflurane combined with esmolol or dexmedetomidine during tympanoplasty in adults: A double-blind, randomized, controlled trial. Curr Ther Res Clin Exp 2009;70:197-208.
15. Jamaliya RH, Chinnachamy R, Maliwad J et al., The efficacy and hemodynamic response to Dexmedetomidine as a hypotensive agent in posterior fixation surgery following traumatic spine injury. Journal of Anaesthesiology, Clinical Pharmacology, 2014;30(2):.203-7.
16. Nasreen F, Bano S, Khan RM et al., Dexmedetomidine used to provide hypotensive anesthesia during middle ear surgery. Indian Journal of Otolaryngology and Head & Neck Surgery, 2009;61(3): 205- 207.
17. Vali LF, Gedam NT, Vali AH, Anesthesia management in a giant congenital undifferentiated orbital teratoma: A challenging, rare entity. Indian Anaesthetists Forum, 2017;18: 28-30.
18. Rokhtabnak F, Motlagh SD, Ghodraty M et al., Controlled Hypotension During Rhinoplasty: A Comparison of Dexmedetomidine with Magnesium Sulfate. Anesthesiology and Pain Medicine, 2017;7(6): e64032.
19. Khalifa OSM, Awad OG. A comparative study of dexmedetomidine, magnesium sulphate, or glyceryl trinitrate in deliberate hypotension during functional endoscopic sinus surgery. Ains shans journal of anaesthesiology 2015;8: 320-326.
20. Jamaliya RH, Chinnachamy R, Maliwad J, Deshmukh VP, Shah BJ, et al. (2014) He eټcacy and hemodynamic response to Dexmedetomidine as a hypotensive agent in posterior fixation surgery following traumatic spine injury. J Anaesthesiol Clin Pharmacol 30: 203-207.
21. Durmus M, But AK, Dogan Z, Yucel A, Miman MC, Ersoy MO. Effect of dexmedetomidine on bleeding during tympanoplasty or septoplasty. Eur J Anaesthesiol. 2007;24:447–53
22. Guggiari M, Dagreou F, Lienhart A et al., Use of nitroglycerine to produce controlled decreases in mean arterial pressure to less than 50 mm Hg. Br J Anaesth., 1985;57(2): 142-147.
23. Tobias JD. Controlled hypotension in children: A critical review of available agents. Paediatr Drugs 2002;4:439-53.
24. Baker AR, Baker AB. Anaesthesia for endoscopic sinus surgery. Acta Anaesthesiol Scand 2010;54:795-803.

Source of Support:Nil
Conflict of Interest: Nil