DISCUSSION

Induction of anaethesia and tracheal intubation may cause profound alteration of haemodynamic state of the patient consequent to both the effects of anesthetic drugs administrated preoperatively and the adrenergic state of the patient.

Stress response to laryngoscopy and intubation has always been concern especially for the cardiac patient.

Direct laryngoscopy and intubation produces maximum pressor response to the direct stimulation of pharyngeal structures[62]. The pressor response may be especially deleterious in patients with preexisting myocardial ischemia and cerebral insufficiency.

The present study was carried to compare the effect of premedication with single oral dose of 150 mg pregabalin versus 0.2 mg clonidine on haemodynamic response to tracheal intubation and the level of preoperative sedation was also compared.

The study was done on 40 patients belonging to ASA I and ASA II classification divided into two groups:

Group I: Patients received 150 mg pregabalin orally 90 minutes before operation.

Group II: Patients received 0.2 mg clonidine orally 90 minutes before operation.

Comparison between the two groups as regards age and sex showed no statistical difference.

Comparison between the two groups as regards haemodynamics as heart rate and mean arterial blood pressure showed that clonidine and pregabalin effectively decreased the haemodynamic changes that occur during the stress response to endotracheal intubation (and this decrease didn't need any treatment).

Clonidine showed significantly more decrease of the rise in heart rate and mean arterial blood pressure than the pregabalin.

Similar to the present study Oddby-Muhrbeck et al [63], found in the study carried out on 68 patients undergoing breast cancer surgery under general anaesthesia that statistically significant difference in the heart rate and mean arterial blood pressure between the group that received clonidine and the group that received placebo. They explained their results on basis that clonidine decrease sympathetic flow.

Yu et al[64], investigated the clinical efficacy of oral clonidine premedication in anaesthesia and analgesia on 32 patients undergoing laparoscopic cholecystectomy, out of which 16 patients received 150 µg clonidine orally and the other 16 patients received placebo before anaesthesia. The authors found that oral clonidine provide a stable heart rate.

Yotsui [65], observed the systolic blood pressure lower in the clonidine group than in the placebo group immediately after endotracheal intubation and after extubation where clonidine group received 4 µg/ kg orally 2 hours before induction of anaesthesia.

Sung et al [66], investigated the clinical efficiency of oral clonidine premedication in anaesthesia and analgesia in patients undergoing laparoscopic cholecystectomy where the clonidine group were premedicated with oral clonidine 150 µg prior to anaesthesia. There was greater haemodynamic stability perioperative compared to placebo.

Singh and Arora[67] studied the clinical efficacy of oral clonidine premedication in patients undergoing laparoscopic cholecystectomies. Fifty patients scheduled for elective laparoscopic cholecystectomy under general anaesthesia were randomly allocated to receive premedication with either oral clonidine 150 µg or placebo 90 minutes prior to induction. Oral clonidine was found to be significantly better in terms of maintaining stable haemodynamics, having an isoflurane sparing effect and having a prolonged time interval to the first request of analgesia postoperatively compared to the control group. Administration of oral clonidine 150 µg as a pre-medicant in patients undergoing laparoscopic cholecystectomy resulted in improved perioperative haemodynamic stability and a reduction in the intra-operative anaesthetic and post-operative analgesic requirements.

Talebi et al [68] studied the efficacy of pre-anaesthetic orally administration of clonidine on pulse rate and blood pressure due to stress response of laryngoscopy and tracheal intubation. The clonidine group showed a significant superiority over placebo in the prevention of increase in systolic blood pressure as well as heart rate during the intubation.

Whitwam et al [69] , found in a study carried out on 48 patients scheduled for day case surgery under general anaesthesia that there was significant difference in the heart rate and mean arterial blood pressure between those who received clonidine 4 µg/ kg iv prior to surgery and those who received placebo.

In the present study the haemodynamic stability of clonidine may be explained by[17]: sympatholysis mediated by the CNS alpha-2 adrenoceptor subtype.Alpha-2-adrenoceptor agonists appear to attenuate the CNS "set-point" at which blood pressure is regulated. The sustained decrease in blood pressure and heart rate are thought to be due to increased parasympathetic (vagal) activity, a centrally-mediated inhibition of the locus ceruleus adrenoceptors, or decreased norepinephrine release at the neuroeffector junction.Imidazoline receptors in the brainstem may also be involved in increasing vagal tone.

However, few data did address the correlation between pre-operative pregabalin administration and the reduction in haemodynamic pressor response to airway instrumentation, during different operative surgeries; of these, the one conducted by Gupta et al[70] in relation to elective laparoscopic cholecystectomy.[71] All such studies did agree on the benefits of the drug, to significantly decrease the significant increase in heart rate and blood pressure provoked by the noxious painful and stressing stimuli of laryngoscopy and intubation[70,71,72,73] Through different perspectives. More-over the attenuation was pertained stabilized with minimal haemodynamic fluctuations, where blood pressure remained significantly reduced throughout the intra-operative period.[70,71]

The explanations set by Rastogi et al and Gupta et al for pregabalin utility in ameliorating such pressor responses were based on their simultaneous findings of pre-operative dose-related sedation induced by the drug in their study series.[70, 71]

One is in favor to adopt reasoning the haemodynamic stability encountered, to the anxiolytic potentialities of pregabalin, raised in previous literature as that of Lauria-Horner and Pohl[75] and Baldwin et al.[76] This aside its pain ameliorating properties currently observed and previously established using the same tested pregabalin dose in different clinical trials as that of Agarwal et al,[77] Cabrera Schulmeyer et al,[78] and Freedman and O'Hara. [79]

Also Sundar AS et al studied the effects of preemptive pregabalin on attenuation of stress response to endotracheal intubation and opioid sparing effect in patients undergoing off pump CABG, the study showed that a single oral dose of 150 mg pregabalin given one hour before surgery attenuated the pressor response in adults.[80]

In the present study the haemodynamic stability of pregabalin may be explained by[29,34,46,47].

Pregabalin transiently inhibit Ca influx, thereby reducing release of several neurotransmitters like glutamate, norepinephrine, serotonin, dopamine, substance P and CGRP.

Comparison between pregabalin and clonidine as regard sedation:

The present study found that both pregabalin and clonidine cause significant degree of sedation but pregabalin causes higher level of sedation than clonidine.

Similar to the present study White PF et al studied the effect of pregabalin on preoperative anxiety and sedation levels. The study showed pre operative pregabalin administration 75 mg to 300 mg oral increased pre operative sedation in dose related fashion.[81]

Gonano C et al studied the anxiolytic effect of pregabalin in outpatient undergoing minor orthopaedic surgery.the study showed that single preoperative dose of 300 mg pregabalin reduced anxiety in these patients.[82]

In the present study this may be explained by presynaptic inhibition of ca influx causing decrease release of several neurotransmitters like glutamate, norepinephrine, serotonin, dopamine, substance P and CGRP[29,34,46,47].

Similar to the present study Fanini et al [83] in their clinical trial, 40 patients, aged 16-64 year, underwent conservative, or prosthetic, or dental surgery procedures, received placebo or 150 micrograms of oral clonidine 90 min before the estimated time of induction of local anesthesia.. Clonidine produced significant sedation as well as significant difference in postoperative pain scores compared to placebo. Systolic blood pressure decreased significantly only after 120 to 150 min following clonidine pretreatment, but none of the patients were treated for hypotension.

Macpherson et al [84] studied the effect of 300 mcg oral clonidine versus 200 mg oral labetalol in laparoscopic cholecystectomy they found that the sedation score significantly raised in the clonidine group compared to the labetalol group.

Laurito CE et al studied the effectiveness of oral clonidine as a sedative /anxiolytic and as a drug to blunt the haemodynamic response to laryngoscopy, the study concluded

that oral clonidine 0.2 mg was effective in reducing the level of behavioral and haemodynamic responses pre operatively and in blunting systolic hypertension produced by laryngoscoby[85]

Kumkum gupta studed oral premedication by clonidine for hemodynamic stability during laryngoscopy and laparoscopic cholecystectomy and found that pregabalin and clonidine caused sedation and anxiolysis with hemodynamic stability.[71]

In contrast to the present study Singh and arura [67] found that no significant difference of the sedation score between oral clonidine and the placebo group this may be explained by a smaller dose of clonidine (150 µg) used in that study.

Also, Samantary et al [86] found in their study that there was no significant difference of the sedation score between oral clonidine and the placebo group. This may be explained by time of sedation score assessment was done after prolonged time than the present study.

SUMMARY

Induction of anaethesia and tracheal intubation may cause profound alteration of haemodynamic state of the patient consequent to both the effects of anesthetic drugs administrated preoperatively and the adrenergic state of the patient.

Stress response to laryngoscopy and intubation has always been concern especially for the cardiac patient.

Pregabalin, is one of these drugs that is coming into focus. It is a structural derivative of the inhibitory neurotransmitter GABA although it doesn't bind to its receptors or to that of benzodiazepines. It was originally developed as spasmolytic agents. Its anticonvulsant anxiolytic and sleep modulating utility permitted its use as an adjuncts for management of generalized or partial epileptic seizures resistant to conventional therapies. It is well tolerated with good safety profile and minimal adverse events most commonly being dizziness and somneless.

Clonidine is classified as an imidazoline derivative. It is the prototypical alpha-2 receptor agonist. Its primary effect is at central pre- and postsynaptic alpha-2 receptors. It has an alpha-2 to alpha-1 selectivity ratio of 200:1. Clonidine has a half-life of 8 hours, and it is available for oral, transdermal, intramuscular, epidural, and intravenous administration

The present study was carried to compare the effect of premedication with single oral dose of 150 mg pregabalin versus 0.2 mg clonidine on haemodynamic response to tracheal intubation and the level of preoperative sedation was also compared.

The study was done on 40 patients belonging to ASA I and ASA II classification. They were randomly divided into two groups:

Group I: Patients received 150 mg pregabalin orally 90 minutes before operation.

Group II: Patients received 0.2 mg clonidine orally 90 minutes before operation.

Comparison between the two groups as regards age and sex showed no statistical difference.

Comparison between the two groups as regards haemodynamics as heart rate and mean arterial blood pressure showed that clonidine and pregabalin effectively decrease the haemodynamic changes that occur during the stress response to endotracheal intubation (and this decrease didn't need to be treated).

Clonidine showed significantly more decrease in heart rate and mean arterial blood pressure than the pregabalin.

Comparison between pregabalin and clonidine as regard sedation:

The present study found that both pregabalin and clonidine cause significant degree of sedation but pregabalin causes higher level of sedation than clonidine.

CONCLUSION

1. Premedication with 150 mg oral pregabalin or 0.2 mg oral clonidine in ASA I and ASA II patients had been found to be relatively safe and effective method to protect against stress response triggered by laryngoscopy.
2. Oral clonidine is better than oral pregabalin in decrease the haemodynamic changes that occur in response to endotracheal intubation.
3. Oral pregabalin is better than oral clonidine in preoperative sedation.

RECOMMENDATIONS

1- 0.2 mg oral clonidine or 150 mg pregabalin can be recommended as premedication for all surgeries using general anaesthesia in healthy patients.

2- Further studies are required to find out the efficacy of these drugs in elderly patients, ASA III, IV patients particularly with compromised cardiovascular and neurological function.

3- The need for more clinical studies to identify the analgesic role of these drugs.

4- Further studies to identify the post operative side effects of these drugs.

5- Further studies to identify the efficacy of different doses of these drugs.

REFERENCES

1. Dorsch JA, Dorsch SE. Understanding anaesthesia equipment: construction, care and complications. 5th ed. Baltimore: Williams and Wilkins; 2007.

2. Kihara S, Brimacombe J, Yaguchi Y, Watanabe S, Taguchi N, Komatsuzaki T. Hemodynamic responses among three tracheal intubation devices in normotensive and hypertensive patients. Anesth Analg 2003; 96:890-5.

3. Burney RG, Winn R. Increased cerebrospinal fluid pressure during laryngoscopy and intubation for induction of anesthesia. Anesth Analg 1975; 54:687-90. Quoted from: Singh S, Smith JE. Cardiovascular changes after the three stages of nasotracheal intubation. Br J Anaesth 2003;91(5):667-71.

4. Kahl M, Eberhart LH, Behnke H, Sänger S, Schwarz U, Vogt S, et al. Stress response to tracheal intubation in patients undergoing coronary artery surgery: direct laryngoscopy versus an intubating laryngeal mask airway. J Cardiothorac Vasc Aneth 2004; 18: 275-80.

5. Noor-Zairul M, Khairul Faizi A. Comparison of the VBM laryngeal tube and laryngeal mask airway for ventilation during manual inline neck stabilisation. Singapore Med J 2006; 47: 892-6.

6. Fox EJ, Sklar CS, Hill CH, Villanueva R, King BD. Complication related to the pressor response to endotracheal intubation. Anesthesiology 1977; 47: 524-5. Quoted from: Tabari M, Alipour M, Ahmadi M. Hemodynamic changes occurring with tracheal intubation by direct laryngoscopy compared with intubating laryngeal mask airway in adults: a randomized comparison trial. Egyptian J Anaesth 2013; 29(2):103–7.

7. Akhlagh SH, Vaziri MT, Masoumi T, Anbardan SJ. Hemodynamic response to tracheal intubation via direct laryngoscopy and intubating laryngeal mask airway (ILMA) in patients undergoing coronary artery bypass graft (CABG). Middle East J Anaesthesiol 2011;21(1):99-103.

8. Shribman AJ, Smith G, Achola KJ. Cardiovascular and catecholamine responses to laryngoscopy with and without tracheal intubation. Br J Anaesth 1987; 59: 295-9.

9. Bucx MJ, Scheck PA, Van Geel RT, Den Ouden AH, Niesing R. Measurement of forces during laryngoscopy. Anaesthesia 1992; 47: 348-51.

10. Aitkenhead AR, Rowbotham DJ, Smith G. Text book of Anaesthesia. 4th ed. New York: Churchill Livingstone; 2001.

11. Deem SA, Bishop MJ, Bedford RF. Physiologic and pathophysiologic responses to intubation. In: Hagberg CA (ed). Benumof's Airway Management. 2nd ed. Philadelphia: Mosby; 2007. 193-212.

12. Guyton AC, Hall JE. Textbook of medical physiology. 11th ed. Philadelphia: Elsevier Saunders Company; 2000.

13. Alizadeh R, Mireskandari SM, Azarshahin M, Darabi ME, Padmehr R, Jafarzadeh A, et al. Oral clonidine premedication reduces nausea and vomiting in children after appendectomy. Iran J Ped 2012; 22(3):399-403.

14. Mohamed SA, Abdel-Ghaffar HS. Effect of the addition of clonidine to locally administered bupivacaine on acute and chronic postmastectomy pain. J Clin Anesth 2013;25(1):20-7.

15. Saravana Babu M, Verma AK, Agarwal A, Tyagi CM, Upadhyay M, Tripathi S. A comparative study in the post-operative spine surgeries: Epidural ropivacaine with dexmedetomidine and ropivacaine with clonidine for post-operative analgesia. Ind J Anaesth 2013;57(4):371-6.

16. Sameenakousar M, Srinivasan KV. Comparison of fentanyl and clonidine for attenuation of the haemodynamic response to laryngocopy and endotracheal intubation. J Clin Diagn Res 2013;7(1):106-11.

17. Cividjian A, Toader E, Wesseling KH, Karemaker JM, McAllen R, Quintin L. Effect of clonidine on cardiac baroreflex delay in humans and rats. Am J Physiol Regul Integr Comp Physiol 2011;300(4):R949-57.

18. Pichot C, Ghignone M, Quintin L. Dexmedetomidine and clonidine: from second- to first-line sedative agents in the critical care setting?. J Int Care Med 2012;27(4):219-37.

19. Lidbrink P. The effect of lesions of ascending noradrenaline pathways on sleep and waking in the rat. Br Res 1974; 74(1):19-40.

20. Bajwa SJ, Bajwa SK, Kaur J, Singh G, Arora V, Gupta S, et al. Dexmedetomidine and clonidine in epidural anaesthesia: a comparative evaluation. Ind J Anaesth 2011;55(2):116-21.

21. Davidson A, McKenzie I. Distress at induction: prevention and consequences. Curr Opin Anaesth 2011;24(3):301-6.

22. Kuczkowski KM. Subarachnoid clonidine for labor pain: the two sides of the coin. J Matern Fetal Neonat Med 2012;25(5):550.

23. Vukovic J, Ramakrishnan P, Milan Z. Does epidural clonidine improve postoperative analgesia in major vascular surgery?. Medicinski glasnik 2012; 9(1):49-55.

24. Joshi SA, Khadke VV, Subhedar RD, Patil AW, Motghare VM. Comparative evaluation of intrathecal midazolam and low dose clonidine: efficacy, safety and duration of analgesia: a randomized, double blind, prospective clinical trial. Ind J Pharmac 2012; 44(3):357-61.

25. Taylor CP, Gee NS, Su TZ, Kocsis JD, Welty DF, Brown JP, et al. A summary of mechanistic hypotheses of gabapentin pharmacology. Epilepsy Res 1998; 29(3):233-49.

26. Lanneau C, Green A, Hirst W, Wise A, Brown J, Donnier E, et al. Gabapentin is not a GABA B receptor agonist. Neuropharmacology 2001; 41:965-75.

27. Gajraj NM. Pregabalin: its pharmacology and use in pain management. Anesth Analg 2007; 105(6):1805-15.

28. Bryans JS, Wustrow DJ. Substituted GABA analogs with central nervous system activity: a review. Med Res Rev 1999; 19:149-77.

29. Ben-Menachem E. Pregabalin pharmacology and its relevance to clinical practice. Epilepsia 2004; 45:13-8.

30. Shneker BF, McAuley JW. Pregabalin: a new neuromodulator with broad therapeutic indications. Ann Pharmacother 2005; 39:2029-37.

31. Field MJ, Holloman EF, McCleary S, Hughes J, Singh L. Evaluation of gabapentin and S-(+)-3-isobutylgaba in a rat model of postoperative pain. J Pharmacol Exp Ther 1997; 282:1242-6.

32. Houghton AK, Lu Y, Westlund KN. S-(+)-3-Isobutylgaba and its stereoisomer reduces the amount of inflammation and hyperalgesia in an acute arthritis model in the rat. J Pharmacol Exp Ther 1998; 285:533-8.

33. Moore RA, Straube S, Wiffen PJ, Derry S, McQuay HJ. Pregabalin for acute and chronic pain in adults. Cochrane Database Syst Rev 2009; 8:CD007076.

34. Baidya DK, Agarwal A, Khanna P, Arora MK. Pregabalin in acute and chronic pain. J Anaesthesiol Clin Pharmacol 2011; 27(3):307-14.

35. Bockbrader H, Hunt T, Strand J, Posvar E, Sedman A. Pregabalin pharmacokinetics and safety in healthy volunteers: results from two phase 1 studies. Neurology 2000; 54:A421

36. Rose MA, Kam PC. Gabapentin: pharmacology and its use in pain management. Anaesthesia 2002; 57:451-62.

37. Stanford SP, Arnold LM. Use of antiepileptics in fibromyalgia. In: McElroy SL, Keck PE, Post RM (eds). Antiepileptic drugs to treat psychiatric disorders. USA: Informa-Health Care Inc; 2008. 363-76.

38. Randinitis EJ, Posvar EL, Alvey CW, Sedman AJ, Cook JA, Bockbrader HN. Pharmacokinetics of pregabalin in subjects with various degrees of renal function. J Clin Pharmacol 2003; 43: 277-83.

39. Arikkath J, Campbell KP. Auxiliary subunits: essential components of the voltage-gated calcium channel complex. Curr Opin Neurobiol 2003; 13(3):298-307.

40. Gazulla J, Tintore M. The P/Q-type voltage-dependent calcium channel as pharmacological target in spinocerebellar ataxia type 6: gabapentin and pregabalin may be of therapeutic benefit. Med Hypotheses 2007; 68:131-6.

41. Bian F, Li Z, Offord J, Davis M, McCormick J, Taylor C. Calcium channel α(2)-δ type 1 subunit is the major binding protein for pregabalin in neocortex, hippocampus, amygdala and spinal cord: an ex vivo autoradiographic study in α(2)-δ type 1 genetically modified mice. Brain Res 2006; 1:1-6.

42. Belliotti T, Capiris T, Ekhato I, Kinsora J, Field M, Heffner T, et al. Structure-activity relationships of pregabalin and analogues that target the α(2)-δ protein. J Med Chem 2005; 48:2294-307.

43. Brust PF, Simerson S, McCue AF, Deal CR, Schoonmaker S, Williams ME, et al. Human neuronal voltage-dependent calcium channels: studies on subunit structure and role in channel assembly. Neuropharmacology 1993; 32:1089-102.

44. Perret D, Luo ZD. Targeting voltage-gated calcium channels for neuropathic pain management. Neurotherapeutics 2009; 6(4):679-92.

45. Kang MG, Felix R, Campbell KP. Long-term regulation of voltage-gated Ca(2+) channels by gabapentin. FEBS Lett 2002; 528:177-82.

46. Errante L, Petroff OA. Acute effects of gabapentin and pregabalin on rat forebrain cellular GABA, glutamate and glutamine concentrations. Seizure 2003; 12:300-6.

47. Micheva KD, Taylor CP, Smith SJ. Pregabalin reduces the release of synaptic vesicles from cultured hippocampal neurons. Mol Pharmacol 2006; 70:467-76.

48. Chizh BA, Gohring M, Troster A, Quartey GK, Schmelz M, Koppert W. Effects of oral pregabalin and aprepitant on pain and central sensitization in the electrical hyperalgesia model in human volunteers. Br J Anaesth 2007; 98:246-54.

49. McClelland D, Evans R, Barkworth L, Martin D, Scott R. A study comparing the actions of gabapentin and pregabalin on the electrophysiological properties of cultured DRG neurones from neonatal rats. BMC Pharmacol 2004; 4:14.

50. Lauria-Horner BA, Pohl RB. Pregabalin: a new anxiolytic. Expert Opin Investig Drugs 2003; 12:663-72.

51. Freynhagen R, Strojek K, Griesing T, Whalen E, Balkenohl M. Efficacy of pregabalin in neuropathic pain evaluated in a 12-week, randomised, double-blind, multicentre, placebo-controlled trial of flexible- and fixed-dose regimens. Pain 2005; 115(3):254-63.

52. Pfizer Company. Lyrica® (pregabalin): Capsules CV [package insert].. New York, NY: Pfizer Inc; 2005.

53. Huppertz HJ, Feuerstein TJ, Schulze-Bonhage A. Myoclonus in epilepsy patients with anticonvulsive add-on therapy with pregabalin. Epilepsia 2001; 42:790-2.

54. Heckmann J, Ulrich K, Dutsch M, Neundorfer B. Pregabalin associated asterixis. Am J Phys Med Rehabil 2005; 84:724.

55. Malaga I, Sanmarti FX. Two cases of painful gynecomastia and lower extremity pain in association with pregabalin therapy. Epilepsia 2006; 47:1576-9.

56. Perucca E. Clinically relevant drug interactions with antiepileptic drugs. Br J Clin Pharmacol 2006; 61:246-55.

57. Brodie MJ, Wilson EA, Wesche DL, Alvey CW, Randinitis EJ, Posvar EL, et al. Pregabalin drug interaction studies: lack of effect on the pharmacokinetics of carbamazepine, phenytoin, lamotrigine and valproate in patients with partial epilepsy. Epilepsia 2005; 46:1407-13.

58. Aldrete JA. The post-anesthesia recovery score revisited. J Clin Anesth 1995;7:89-91.

59. Grant S, Aitchison T, Henderson E, Christie J, Zare S, McMurray J, et al. A comparison of the reproducibility and the sensitivity to change of visual analogue scales, Borg scales, and Likert scales in normal subjects during submaximal exercise. Chest 1999; 116(5):1208-17.

60. Kotz S, Balakrishnan N, Read CB, Vidakovic B. Encyclopedia of statistical sciences. 2nd ed. Hoboken, New Jersey: Wiley-Interscience; 2006.

61. Kirkpatrick LA, Feeney BC. A simple guide to IBM SPSS statistics for version 20.0. Student ed. Belmont, Calif.: Wadsworth, Cengage Learning; 2013.

62. Weinger MB, Vredenburgh AG, Schumann CM, Macario A, William KJ, Kalsher MJ, et al. Quantitative description of the workload associated with airway management procedures. J Clin Anesth 2000; 12: 273-82.

63. Oddby-Muhrbeck E, Eksborg S, Bergendahl HT, Muhrbeck O, Lonnqvist PA. Effects of clonidine on postoperative nausea and vomiting in breast cancer surgery. Anesthesiology 2002; 96(5):1109-14.

64. Yu HP, Hseu SS, Yien HW, Teng YH, Chan KH. Oral clonidine premedication preserves heart rate variability for patients undergoing larparoscopic cholecystectomy. Acta Anaesthesiol Scand 2003;47(2): 185-90.

65. Yotsui T. Clonidine premedication prevents sympathetic hyperactivity but does not prevent hypothalamo-pituitary-adrenocortical responses in patients undergoing laparoscopic cholecystectomy. J Anesthesia 2001; 15(2):78-82.

66. Sung CS, Lin SH, Chan KH, Chang WK, Chow LH, Lee TY. Effect of oral clonidine premedication on perioperative hemodynamic response and postoperative analgesic requirement for patients undergoing laparoscopic cholecystectomy. Acta Anaesthesiol Sinica 2000; 38(1):23-9.

67. Singh S, Arora K. Effect of oral clonidine premedication on perioperative haemodynamic response and postoperative analgesic requirement for patients undergoing laparoscopic cholecystectomy. Indian J Anaesthesia 2011; 55(1):26-30.

68. Talebi H, Nourozi A, Fateh S, Mohammadzadeh A, Eghtesadi-Araghi P, Jabbari S, et al. Effects of oral clonidine premedication on haemodynamic response to laryngoscopy and tracheal intubation: a clinical trial. Pakistan J Biol Sci 2010; 13(23):1146-50.

69. Whitwam JG. Co-induction of anaesthesia: day-case surgery. Eur J Anaesthesiol Suppl 1995;12:25-34.

70. Rastogi B, Gupta K, Gupta PK, Agarwal S, Jain M, Chauhan H. Oral pregabalin premedication for attenuation of haemodynamic pressor response of airway instrumentation during general anaesthesia: a dose response study. Indian J Anaesth 2012; 56(1): 49–54.

71. Gupta K, Sharma D, Gupta PK. Oral premedication with pregabalin or clonidine for hemodynamic stability during laryngoscopy and laparoscopic cholecystectomy: a comparative evaluation. Saudi J Anaesth 2011; 5(2):179-84.

72. Prys Roberts C, Green LT, Meloche R, Foex P. Studies of anaesthesia in relation to hypertension II, hemodynamic consequences of induction and endotracheal intubation. Br Anaesth 1971; 43:531-47.

73. Russell WJ, Morris RG, Frewin DB, Drew SE. Changes in plasma catecholamine concentrations during endotracheal intubation. Br J Anaesth 1981; 53(8):837-9.

74. Shribman AJ, Smith G, Achola KJ. Cardiovascular and catecholamine response to laryngoscopy with and without tracheal intubation. Br J Anaesth 1987; 59:295-9.

75. Lauria-Horner BA, Pohl RB. Pregabalin: a new anxiolytic. Expert Opin Investig Drugs 2003; 12:663-72.

76. Baldwin DS, Ajel K. Role of pregabalin in the treatment of generalized anxiety disorder. Neuropsychiatr Dis Treat 2007; 3(2):185-91.

77. Agarwal A, Gautam S, Gupta D, Agarwal S, Singh PK, Singh U. Evaluation of a single preoperative dose of pregabalin for attenuation of postoperative pain after laparoscopic cholecystectomy. Br J Anaesth 2008; 101(5):700-4.

78. Cabrera-Schulmeyer MC, De la-Maza J, Ovalle C, Farias C, Vives I. Analgesic effects of a single pre-operative dose of pregabalin after laparoscopic sleeve gastrectomy. Obes Surg 2010; 20:1678-81.

79. Freedman BM, O'Hara E. Pregabalin has opioid-sparing effects following augmentation mammaplasty. Aesthet Surg J 2008; 28:421-4.

80. Sundar AS, Kodali R, Sulaiman S, Ravullapalli H, Karthekeyan R, Vakamudi M. The effects of preemptive pregabalin on attenuation of stress response to endotracheal intubation and opioid-sparing effect in patients undergoing off-pump coronary artery bypass grafting. Ann Card Anaesth 2012; 15(1):18-25.

81. White PF, Tufanogullari B, Taylor J, Klein K. The effect of pregabalin on preoperative anxiety and sedation levels: a dose-ranging study. Anesth Analg 2009; 108(4):1140-5.

82. Gonano C, Latzke D, Sabeti-Aschraf M, Kettner SC, Chiari A, Gustorff B. The anxiolytic effect of pregabalin in outpatients undergoing minor orthopaedic surgery. J Psychopharmacol 2011; 25(2): 249-53.

83. Fanini D, Poglio M, Marci MC, Iovinelli G, Antenucci F. Oral premedication with clonidine as an alternative in dental practice. The effects on the pain threshold, blood pressure and salivary flow. Minerva Stomatol 1998;47(9):453-64.

84. Macpherson J. Kennedy RR, Gin T. Comparsion of oral premedication for laparoscopic choelcystectomy: labetalol versus clonidine. Anaesth Intensive Care 1997; 25:720.

85. Laurito CE, Baughman VL, Becker GL, De Silva TW, Carranza CJ. The effectiveness of oral clonidine as a sedative/anxiolytic and as a drug to blunt the hemodynamic responses tolaryngoscopy. J Clin Anesth 1991; 3(3):186-93.

86. Samantaray A, Rao MH, Chandra A. The effect on post-operative pain of intravenous clonidine given before induction of anaesthesia. Indian J Anaesth 2012;56(4):359-64.

الملخص العربى

تنبيب القصبه الهوائيه هى تقنيه آمنه و بسيطه و سريعه تهدف الى المحافظه على بقاء الممرات الهوائيه مفتوحه و حمايه الرئتين من دخول بقايا محتويات المعده وكذلك هى ضروريه لوضع المريض على جهاز التنفس الصناعى.

ولكن التنبيب الرغامى يتسبب فى ارتفاع ضغط الدم و تسارع نبضات القلب و عدم انتظامها و ارتفاع ضغط المخ . بالرغم من أن هذه الآثار قصيره المدى و لكنها قد تتسبب فى أضرار بالغه لمرضى القلب و الأوعيه الدمويه و مرضى المخ و الأعصاب.

لذلك تم عمل الكثير من الأبحاث العلميه للتوصل لكيفيه تقليل مثل هذه الآثار من ضمنها:

١. تقليل وقت التنبيب الرغامى لأقل فتره ممكنه.
٢. إستخدام مخدر موضعى للممرات الهوائيه.
٣. إعطاء جرعات من المواد الأفيونيه مثل الفينتانيل .
٤. إعطاء أدويه ذات تأثير على القلب و الأوعيه الدمويه مثل عقار إزمولول و عقار نيكارديبين .

و الدراسه الآتيه تركز على تأثير عقارين هما البريجابالين و الكلونيدين.

عقار البريجابالين وهو مشتق من الناقل العصبي المثبط جابا لكنه على الرغم من دلك لا يتحد مع مستقبلات جابا أو جابا ب ولا حتى مستقبلات البنزوديازبين،كما إنه لا يتحول الى جاباولا يؤثر على امتصاصه ولا تكسيره . إن عقار البريجابالين انشئ أصلا كمزيل للتشنج .كما أن فائدته كمزيل للقلق ومحوَر للنوم قد أدى إلى استخدامه كعقار معاون لعلاج نوبات الصرع المعمم أو الجزئي المقاومة للعلاجات التقليدية . وعلاوة على دلك تم توسيع استخداماته العلاجيه مع مرور الوقت للسيطرة على الآلام المزمنة وكدلك بعض حالات الآلام الحادة .وهو دواء سهل الإستعمال وآمن وآثاره الجانبيه محدودة ، وأكثرها شيوعا الدوخة والنعاس.

و يصنف عقار الكلونيدين كايميدازولين. و هو ناهض لمستقبلات ألفا ٢- و تأثيره الأساسى على مستقبلات ألفا- ٢ المركزية ما قبل وبعد التشابك العصبى .و لعقار الكلونيدين نسبة انتقاء لمستقبلات ألفا٢- الى ألفا١- بنسبة ٢٠٠ الى ١.مدة العمر النصفى لعقار الكلونيدين هى ٨ ساعات، و هو متاح للاعطاء عن طريق الفم، عبر الجلد ، عن طريق العضل، فوق الأم الجافية، وعن طريق الوريد.

هذه الدراسه أجريت لمقارنه تأثير البريجابالين عن طريق الفم مقابل الكلونيدين عن طريق الفم ما قبل التخدير على رد الفعل الديناميكى للدوره الدمويه أثناء التنبيب الرغامى للمرضى الذين يجرون العمليات الجراحية البسيطة الإختيارية . قارنت أيضا الدراسة تأثيرهم على التهدئة المحيطة بالجراحة.

وقد أجريت الدراسة على٤٠ مريض ينتمون إلى المستوى الأول أو الثاني في تصنيف الجمعية الأمريكية للتخديرأعمارهم تتراوح بين ١٨و٤٥ سنة من الجنسين .وقد تم استبعاد المرضى المصابين:

(بأمراض في القلب والأوعية الدموية ،اختلال وظائف الكبد والكلى ، المصابون بالسمنة المفرطة ، مدمني الكحول أو الأدوية،من لديهم دلائل على صعوبة التنبيب أو يأخذون أدوية لمعالجة ارتفاع ضغط الدم والإكتئاب.) حيث تم عمل تقييم ما قبل العملية لجميع المرضى من خلال أخذ تاريخ مرضى مفصل، فحص إكلينيكى كامل، تقييم للممرات الهوائية و الفحوص المختبرية الروتينية.

وتم تقسيمهم عشوائيا باستخدام تقنية الظرف المغلق إلى مجموعتين متساويتين :

المجموعة الأولى: تم اعطاء المرضى قرص بريجابالين ١٥٠مليجرام ٩٠ دقيقة قبل ادخال التخدير.

المجموعة الثانية: تم اعطاء المرضى قرص كلونيدين ٠,٢مليجرام ٩٠دقيقة قبل ادخال التخدير.

وقبل اعطاء المرضى الأقراص قد تم تسجيل مؤشراتهم الحيوية من ضغط الدم ،نبضات القلب ، تشبع الدم بالأوكسجين . ثم بعد دخولهم غرفة العمليات تم توصيلهم بجهازقياس المؤشرات الحيوية واخذ قياسات.

وقد خضع جميع المرضى لنفس بروتوكول التخدير كالتالى:-

بدأ التخدير الكلى بإعطاء عقار الفنتانيل بجرعة ١ ميكروجم/ كجم ’عقار البروبوفول ١٪ بجرعة ٢ملجم / كجم تليها جرعة ٠,٢ ملجم / كجم من عقار السيزأتراكيوريم عن طريق الوريد لتسهيل القيام بتنبيب القصبة الهوائية.ثم تم التنبيب في أقل وقت ممكن يتشابه في جميع المرضى وقد تم المحافظة على استمرار التخدير الكلى بإستخدام عقار الأيزوفلورين ١-١,٥٪ في اوكسجين بنسبة ١٠٠٪ مع إعطاء جرعات إضافية من عقار السيزأتراكيوريم بجرعة ٠,٠٢ملجم / كجم كل نصف ساعة حتى انتهاء العملية.

القياسات:

١- **البيانات الديمغرافية:** وتشمل العمر والجنس

٢- **معدلات الدورة الدموية:** وتشمل معدل ضربات القلب،متوسط ضغط الدم الشرياني، وتشبع الأوكسجين الشرياني والتي تم قياسها قبل اعطاء الأقراص وقبل وبعده التخدير،بعد التنبيب، كل دقيقتين حتى مرور ١٠دقائق،كل ١٥ دقيقة حتى نهاية العملية.

نتائج الدراسة :

في هذه الدراسة فيما يتعلق بالسن والجنس لا يوجد فرق كبير بين المجموعتين . أما فيما يتعلق بمعدل نبضات القلب وضغط الدم الشرياني فإن المجموعتين سجلتا انخفاض ملحوظ في هذين المؤشرين في جميع القياسات المأخوذة لكن حدث ارتفاع طفيف عند وقت دقيقتين (أكثر وقت ترتفع فيه المؤشرات الحيوية استجابة للتنبيب) ولكن الإرتفاع لم يصل إلى القيمة الأولية وظل الإنخفاض عنها واضح.ولكن الكلونيدين أفضل من البريجابالين.

أما فيما يتعلق بمستوى السكون: فقد قام العقارين بتهدئة المرضى بشكل ملحوظ ولكن البريجابالين كان أفضل من الكلونيدين.

في ضوء النتيجة السابقة يمكن أن نستنتج الأتي:

١- وقد وجد أن اعطاء ٠,٢ملليجرام من الكلونيدين او ١٥٠ملليجرام من البريجابالين عن طريق الفم قبل التخدير في المرضى الذين ينتمون الى المستوى الأول أو الثانى فى تصنيف الجمعية الأمريكية للتخدير يعتبر طريقة آمنة وفعالة نسبيا للحماية من الأثار الناتجة عن التنبيب.

٢- الكلونيدين أفضل من البريجابالين في تقليل ارتفاع الضغط وتسارع ضربات القلب الناتج عن التنبيب.

٣- البريجابالين أفضل من الكلونيدين في تهدئة المرضى .

في ضوء النتيجة السابقة يمكن أن نوصي بالأتي :

١- يمكن اعطاء ٠,٢منيجرام من الكلونيدين أو ١٥٠مليجرام بريجابالين عن طريق الفم على النحو الموصى به لجميع المرضى ذوى حالة صحية جيدة.
٢- ويلزم إجراء مزيد من الدراسات لمعرفة فعاليته في المرضى كبار السن والمرضى الذين ينتمون إلى الى المستوى الثالث أو الرابع فى تصنيف الجمعية الأمريكية للتخدير خاصة فى وجود خطورة على القلب والأوعية الدموية.
٣- الحاجة لمزيد من الدراسات الطبية للتعرف على دور هذين العقارين في تسكين الألم .
٤- المزيد من الدراسات للتعرف على ما إذا كان هناك أثار جانبية لهذين العقارين بعد العملية.

جامعة الإسكندرية
كلية الطب
قسم التخدير والعناية المركزة الجراحية

تأثير عقار البريجابالين مقابل عقار الكلونيدين على ثبات الديناميكية الدموية أثناء تنبيب القصبة الهوائية

رسالة مقدمة

لقسم التخدير والعناية المركزة الجراحية ـ كلية الطب ـ جامعة الإسكندرية
ضمن متطلبات درجة

الماجستير

فى

التخدير والعناية المركزة الجراحية

مـــن

ولاء محمد مبروك زيدان
بكالوريوس الطب والجراحة ، ٢٠٠٨
كلية الطب، جامعة الإسكندرية

[٢٠١٥]

جامعة الإسكندرية
كلية الطب
قسم التخدير والعناية المركزة الجراحية

تأثير عقار البريجابالين مقابل عقار الكلونيدين على ثبات الديناميكية الدموية أثناء تنبيب القصبة الهوائية

رسالة مقدمة من

ولاء محمد مبروك زيدان

للحصول على درجة

الماجستير

فى

التخدير والعناية المركزة الجراحية

لجنة المناقشة والحكم على الرسالة	**التوقيع**
أ.د/ درية محمد فكرى أستاذ ورئيس قسم التخدير والعناية المركزة الجراحية قسم التخدير والعناية المركزة الجراحية كلية الطب جامعة الإسكندرية	.....
أ.م.د/ عصام عبدالحميد اسماعيل أستاذ مساعد التخدير والعناية المركزة الجراحية قسم التخدير والعناية المركزة الجراحية كلية الطب جامعة المنوفية	.....
أ.م.د/ علا محى الدين زناتى أستاذ مساعد التخدير والعناية المركزة الجراحية قسم التخدير والعناية المركزة الجراحية كلية الطب جامعة الإسكندرية	.....

التاريخ / /

لجنة الإشراف **موافقون**

أ.د/ درية محمد فكرى .....

أستاذ ورئيس قسم التخدير والعناية المركزة الجراحية
قسم التخدير والعناية المركزة الجراحية
كلية الطب
جامعة الإسكندرية

أ.د/ ماهر السيد رمضان .....

أستاذ التخدير والعناية المركزة الجراحية
قسم التخدير والعناية المركزة الجراحية
كلية الطب
جامعة الإسكندرية

المشرف المشارك

د/ محمد شوقى الحديدى .....

مدرس التخدير والعناية المركزة الجراحية
قسم التخدير والعناية المركزة الجراحية
كلية الطب
جامعة الإسكندرية