Original Article

The Comparison of Dexmedetomidine, Esmolol, and Combination of Dexmedetomidine with Esmolol for Attenuation of Sympathomimetic Response to Laryngoscopy and Intubation in Patients Undergoing Coronary Artery Bypass Grafting

Dipali Singh, Sathyanarayan Jagannath, Shio Priye, A Syed Mudassar

Department of Anaesthesiology, Vydehi Institute of Medical Sciences, Bengaluru, Karnataka, India

Abstract

Background: The aim of this study was to compare the effects of dexmedetomidine, esmolol, and combination of both on control of sympathetic response to laryngoscopy and tracheal intubation in coronary artery disease patients. **Material and Methods:** A prospective, randomized, double-blinded clinical study included 90 patients scheduled for elective coronary artery bypass surgery. Patients were randomly allocated into three groups of 30 each: dexmedetomidine group (Group D) 1 μg/kg, esmolol group (Group E) 2 mg/kg, and group dexmedetomidine with esmolol (Group DE) 0.5 μg/kg of dexmedetomidine with 1 mg/kg of esmolol. Each drug was diluted with 0.9% normal saline to 20 ml volume and infused in 10 min before induction of anesthesia. Hemodynamic changes (heart rate [HR], arterial blood pressure, and pulmonary artery pressure) were compared at various time intervals as follows-baseline, after study drug, after induction, and 1, 3, and 5 min after intubation. Statistical analysis included analysis of variance, Chi-square, and Fisher's exact test. **Results:** In Group DE, there was no significant increase in HR at all-time intervals, and the HR was stable compared to Group D and Group E. Blood pressure values were comparable in all groups except in Group E at 5 min. The pulmonary arterial pressures were statistically less in DE group except at 3 and 5 min. **Conclusions:** The combination of dexmedetomidine and esmolol group has beneficial effect on HR and pulmonary arterial pressures but has no additional advantage with respect to arterial blood pressure when compared with dexmedetomidine and esmolol groups in patients undergoing elective coronary artery bypass grafting.

Keywords: *Dexmedetomidine, endotracheal intubation, esmolol, hemodynamic response, laryngoscopy*

Introduction

Airway control during general anesthesia is usually achieved by laryngoscopy and endotracheal intubation which invariably leads to mechanical and chemical stimulation. The mechanical stimulus leads to reflex stimulation of cardiovascular and respiratory systems.[1] This reflex peaks within 1 min and ends in about 5–10 min after intubation. While chemical stimulus activates the sympathetic catecholamines release, leading to hypertension, tachycardia, and arrhythmia.[2,3] The increase in arterial blood pressure begins within 5 s of laryngoscopy and reaches its peak at about 1–2 min.[4] Tachycardia leads to an increase in oxygen consumption of the myocardium, decrease diastolic filling, and reduced coronary blood supply, thereby causing more stress on the myocardium as compared to hypertension.[3]

Myocardial ischemia might occur during the induction/intubation sequence in patients with coronary artery disease. Intraoperative ischemia has been associated with a high rate of perioperative myocardial infarction.[5] A variety of drugs has been used to control this hemodynamic response such as narcotics, alpha-2 agonists, vasodilators, beta blockers, calcium channels blocker, and local anesthetic. However, no modality was devoid of drawbacks and limitations.[4]

Dexmedetomidine is an imidazole derivative and highly selective alpha2-adrenergic receptor agonist, and it produces dose-dependent sedation, anxiolysis, and

How to cite this article: Singh D, Jagannath S, Priye S, Mudassar AS. The comparison of dexmedetomidine, esmolol, and combination of dexmedetomidine with esmolol for attenuation of sympathomimetic response to laryngoscopy and intubation in patients undergoing coronary artery bypass grafting. Ann Card Anaesth 2019;22:353-7.

Address for correspondence:
Prof. Shio Priye, Department of Anaesthesiology, Vydehi Institute of Medical Sciences, Whitefield, Bengaluru - 560 066, Karnataka, India.
E-mail: shiopriye@gmail.com

Access this article online

Website: www.annals.in

DOI: 10.4103/aca.ACA_112_18

Quick Response Code:

analgesia due to its effect on the central adrenergic outflow. Dexmedetomidine is also known to blunt the hemodynamic response to endotracheal intubation resulting in a decrease in the incidence of myocardial is chemia during cardiac surgery.[5]

Esmolol is an ultra-short acting beta-adrenergic receptor antagonist. While it inhibits beta1 receptors of the myocardium, it also inhibits beta2 receptors of smooth muscles of bronchial and vascular walls at higher doses.[6] Esmolol minimizes the increase in HR and myocardial contractility (primary determinants of myocardial oxygen consumption) by attenuating the positive chronotropic and inotropic effects of increased adrenergic activity.[6]

In this study, we compared the effects of dexmedetomidine, esmolol, and the combination of both on control of hemodynamic response to tracheal intubation in patients with coronary artery disease.

Materials and Methods

A prospective, randomized, double-blind clinical study was designed with a total of 90 patients scheduled for elective coronary artery bypass grafting (CABG) between the ages of 21–65 years. The study was conducted between August 2015 and October 2016 after receiving approval by the Institutional Ethical Committee. This trial was registered at Clinical Trials Registry-India (CTRI) ctri.nic.in under number CTRI/2017/11/010355. A written informed consent was obtained from all the patients. Exclusion criteria included anticipated difficult intubation, emergency surgery, left ventricular ejection fraction <40%, left ventricular aneurysm, associated valvular lesions, left main coronary artery disease, severe systemic diseases involving the renal and hepatic systems, preoperative left bundle branch block, chronic obstructive pulmonary disease, and intubation attempt lasting longer than 20 s.

All the patients were evaluated before surgery. Angiotensin-converting enzyme inhibitors, diuretics, and calcium channel blockers were stopped on the day of surgery and beta blockers were continued to the day of surgery as per our institutional protocol. All the patients received oral alprazolam 0.5 mg and ranitidine 150 mg the night before and 2 h before surgery.

All the patients were randomly allocated to three groups of 30 each with the help of computer-generated table of random numbers to receive following drugs before induction: Group dexmedetomidine(Group D, n = 30) received 1 μg/kg of dexmedetomidine, Group esmolol (Group E, n = 30) received 2 mg/kg of esmolol, Group dexmedetomidine and esmolol (Group DE, n = 30) received 0.5 μg/kg of dexmedetomidine and esmolol 1 mg/kg. All the study drugs were diluted to a total volume of 20 ml with normal saline (0.9%) and were given as intravenous (IV) infusion over a period of 10 min. All the drugs were prepared in an identical syringe and infused using syringe pump (Injectomat Agilia, Fresenius Kabi, France) by an independent anesthesiologist not aware of the study. We avoided placebo group in our study because the study was on the patient with coronary artery disease and it is well-established fact that laryngoscopy increases the stress response, which is detrimental to such patients.

In the operation room under local anesthesia peripheral venous, central venous and arterial cannulation was performed. Electrocardiogram, pulse oximetry, intra-arterial pressure, pulmonary arterial pressure, nasopharyngeal temperature, urine output, and capnography were monitored.

After the study drug infusion, general anesthesia was given using midazolam 40 μg/kg IV, fentanyl 3 μg/kg IV, and etomidate 0.3 mg/kg IV. Lack of verbal command was considered as the end-point of induction. Neuromuscular blockade was achieved by rocuronium bromide 1 mg/kg IV to facilitate intubation with appropriate size cuffed endotracheal tube after 2 min of mask ventilation by a single operator in all the cases.

Heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), systolic pulmonary arterial pressure (SPAP), diastolic pulmonary arterial pressure (DPAP), and mean pulmonary arterial pressure (MPAP) were recorded. These parameters were recorded as follows: B-baseline, before the start of infusion of study drugs; AD-after the study drug infusion; AI-2 min after induction and just before intubation; 1 min/min after intubation; 3 min/min after intubation; and 5–5 min after intubation.

Significant hypotension was defined in this study as SBP <25% of baseline value. Significant bradycardia was defined as HR <50 beats/min. None of the patients met the above-said definition and needed intervention. There was no change in the study design after the commencement of the study and no dropouts from the study.

Based on outcome variables, namely MAP with least mean difference 10 mmHg, the sample size of 30 in each group was adequate for this study (with 90% statistical power and 5% level of significance). Descriptive and inferential statistical analysis has been carried out in the present study. Results on continuous measurements are presented on mean ± standard deviation (Min-Max) and results on categorical measurements are presented in Number (%). Analysis of variance has been used to find the significance of study parameters between three or more groups of patients; Chi-square/Fisher's Exact test has been used to find the significance of study parameters on the categorical scale between two or more groups. The statistical software, namely SPSS 18.0 (SPSS Inc., Chicago, USA), and R environment ver. 3.2.2 were used for the analysis of the data. $P < 0.05$ was considered statistically significant.

Results

A total of 96 patients were assessed for the eligibility, out of which 90 patients were included in the study after randomization to complete the study. Six patients were not included in this study because of patient's refusal. There was no significant difference among the groups with regard to demographic variables as well as risk factors and preoperative cardiovascular medications [Table 1]. Baseline hemodynamic parameters were comparable in all the groups.

There was a statistically significant difference in HR seen in Group DE after administration of the drug, after induction and at 1, 3, and 5 min after intubation ($P < 0.05$) [Table 2]. There was no significant difference in SBP, DBP, and MAP between the groups except for a statistically significant decrease in DBP and MAP at 5 min after intubation in Group E [Table 3]. The SPAP, DPAP, and MPA *P* values were significantly lower in the DE group after study drug infusion and at all times intervals of observation ($P < 0.05$) except at 1 and 3 min in SPAP and at 3 min after intubation in DPAP [Table 4].

Discussion

Laryngoscopy and endotracheal intubation during general anesthesia cause a significant hemodynamic disturbance due to the stimulation of the sympathoadrenal system. For patients, especially who are undergoing CABG surgery, tachycardia and hypertension due to the stress of laryngoscopy and intubation increase the risk of perioperative myocardial ischemia and infarction.

It has been noted that rise in blood pressure and HR manifests during direct laryngoscopy for tracheal intubation after 15 s and reach peak if laryngoscopy is continued for 30–45 s.[6] In our study, the duration of laryngotracheal intubation was limited to 20 s.

Table 1: Demographic, comorbidity, and medication

Variable	Group D	Group E	Group DE	*P*
Age (year)	56.2±6.1	56.7±7.1	55.2±10.3	0.774
Weight (kg)	60.4±5.0	60.9±5.9	61.8±7.9	0.696
Male/female	17/13	19/11	20/10	0.718
NYHA II/III	20/10	21/09	19/11	0.960
Hypertension	17	20	17	0.659
Diabetes mellitus	18	21	21	0.638
Ejection fractions	52.6±6.3	54.3±5.6	55.6±5.3	0.139
Beta-blockers	21	19	21	0.816
Number coronary arteries diseased (1/2/3)	4/6/20	4/4/22	2/6/22	0.86

Values are expressed as mean±SD or number of patients. No significant intergroup difference was found. *P* value represented between groups: One-way ANOVA test, Chi-square test, and Fisher's exact test. ANOVA: Analysis of variance, SD: Standard deviation, Group D: Dexmedetomidine, Group E: Esmolol, Group DE: Dexmedetomidine and esmolol, NYHA: New York Heart Association

Most of the previous clinical studies have compared only blood pressure and HR at different time intervals before and after laryngoscopy. In our study, we compared pulmonary artery pressures in addition to arterial blood pressure and HR to better understand the hemodynamic changes associated with study drugs.

Dexmedetomidine has analgesic and sedative effects in addition to blunting the hemodynamic response to endotracheal intubation and shown to reduce the extent of myocardial ischemia during cardiac surgery.[5] Esmolol minimizes the increase in HR and myocardial contractility (primary determinants of myocardial oxygen consumption) by attenuating the

Table 2: Comparison of heart rate (beats/min)

Time	Group D	Group E	Group DE	*P*
B	78.8±11.9	75.1±10.4	74.1±14.7	0.309
AD	71.8±9.6	72.7±9.1	64.7±13.1	0.009*
AI	69.0±7.1	73.6±9.8	66.2±12.1	0.018*
1 min	78.6±8.5	89.5±17.4	69.4±5.8	<0.001*
3 min	74.8±9.3	83.3±15.5	71.9±11.3	0.002*
5 min	71.9±7.9	81.8±14.3	70.2±10.6	<0.001*

Values are expressed as mean±SD. *Statistically significant ($P<0.05$): One-way ANOVA test. Group D: Dexmedetomidine, Group E: Esmolol, Group DE: Dexmedetomidine and esmolol, ANOVA: Analysis of variance, SD: Standard deviation

Table 3: Comparison of arterial blood pressure (mmHg)

Time	Group D	Group E	Group DE	*P*
SAP				
B	154.5±12.1	156.7±18.5	155.0±18.0	0.870
AD	150.1±19.0	153.2±14.2	146.3±16.2	0.276
AI	136.1±34.3	132.4±18.3	134.5±23.3	0.858
1 min	142.7±34.4	136.5±24.4	135.7±22.0	0.564
3 min	131.2±30.0	128.2±16.9	132.1±24.5	0.812
5 min	126.3±33.1	119.7±16.0	120.4±20.1	0.513
DAP				
B	80.0±10.4	79.7±9.7	78.6±9.0	0.850
AD	77.8±9.4	79.0±6.0	75.9±4.9	0.230
AI	74.4±13.4	71.1±13.6	74.5±8.9	0.472
1 min	75.8±13.7	76.1±11.6	74.7±7.3	0.869
3 min	74.0±18.5	69.3±10.0	73.6±8.9	0.315
5 min	75.1±15.3	65.8±8.5	67.8±8.4	0.005*
MAP				
B	104.7±16.0	105.0±12.6	103.9±11.8	0.943
AD	102.0±16.3	104.9±8.0	99.0±9.1	0.164
AI	94.3±19.9	89.2±15.7	91.6±9.4	0.450
1 min	98.6±19.1	93.9±12.0	92.9±9.2	0.257
3 min	92.1±20.2	86.4±11.9	93.2±14.5	0.211
5 min	92.6±20.1	82.3±10.7	85.2±12.2	0.027*

Values are expressed as mean±SD. *Statistically significant ($P<0.05$) between the groups: One-way ANOVA test. Group D: Dexmedetomidine, Group E: Esmolol, Group DE: Dexmedetomidine and esmolol, SAP: Systolic arterial pressure, DAP: Diastolic arterial pressure, MAP: Mean arterial pressure, ANOVA: Analysis of variance, SD: Standard deviation

Table 4: Comparison of pulmonary artery pressure (mmHg)

	Group D	Group E	Group DE	*P*
SPAP				
B	32.5±7.6	31.1±9.1	30.7±8.1	0.676
AD	30.7±6.1	31.3±6.8	26.7±6.3	0.012*
AI	30.9±4.3	29.1±7.7	26.6±4.5	0.016*
1 min	32.3±3.9	30.2±9.3	28.0±7.5	0.084
3 min	28.2±3.6	27.6±7.2	25.9±4.7	0.263
5 min	28.2±2.6	25.0±7.7	25.2±4.5	0.038*
DPAP				
B	14.6±3.3	12.9±5.9	12.6±4.3	0.204
AD	14.3±2.3	14.3±5.0	10.8±3.2	<0.001*
AI	16.8±2.5	14.1±6.1	11.8±2.3	<0.001*
1 min	16.8±2.2	15.2±7.6	12.4±3.8	0.004*
3 min	14.8±1.8	13.2±4.8	12.4±4.5	0.065
5 min	15.8±1.8	13.0±4.1	12.9±3.5	0.001*
MPAP				
B	20.7±4.5	18.8±6.6	18.7±5.6	0.313
AD	19.7±3.3	19.1±5.0	16.6±4.3	0.014*
AI	21.1±2.3	19.1±6.5	16.4±3.3	<0.001*
1 min	22.2±2.9	19.9±7.4	16.0±4.3	<0.001*
3 min	19.9±2.0	17.9±5.9	16.5±4.0	0.010*
5 min	19.8±1.8	17.7±4.9	16.6±3.5	0.005*

Values are expressed as mean±SD. *Statistically significant (P<0.05) between the groups: One-way ANOVA test. Group D: Dexmedetomidine, Group E: Esmolol, Group DE: Dexmedetomidine and esmolol, SPAP: Systolic pulmonary arterial pressure, DPAP: Diastolic pulmonary arterial pressure, MPAP: Mean pulmonary arterial pressure, ANOVA: Analysis of variance, SD: Standard deviation

positive chronotropic and inotropic effects of increased adrenergic activity.[6]

Various studies have used dexmedetomidine in the dose ranging from 0.5 to 10 μg/kg and concluded that significant bradycardia and hypotension occurred at higher doses.[5,7,8] The hypotension and bradycardia caused by dexmedetomidine, theoretically, could limit its usage in previously beta-blocked ischemia heart patients. A small number of studies have used dexmedetomidine as an anesthetic adjuvant in CABG patients receiving beta blockers and reported that the intraoperative incidence of bradycardia requiring treatment was not more common in the dexmedetomidine group than in the control group.[4,5]

Studies have used dexmedetomidine in the range of 0.5–2 μg/kg to effectively control the hemodynamic responses during laryngoscopy and intubation and have concluded that optimal dose is 1 μg/kg.[4,9-11] The most commonly observed side effects of dexmedetomidine are hypotension and bradycardia that occur more frequently during the loading period. Previous studies have suggested that reducing loading dose and slowing infusion rate may prevent cardiovascular side effects.[10,12] We, therefore, used dexmedetomidine as a slow infusion at 1 μg/kg over 10 min and observed a consistent and reliable protection on HR and blood pressure with no severe side effects and the findings are very much similar to the observations of previous studies.

Esmolol is effective, in a dose-dependent manner, in the attenuation of the sympathomimetic response to laryngoscopy and intubation. There are different doses of esmolol studied in previous studies and the choice of an optimal dose of esmolol is very important to balance between the desired and side effects.[13]

Studies have used esmolol as bolus and infusion in the dose ranging from 0.4 to 2 mg/kg and in combination with other drugs.[13-18] The results are variable and no consensus has been reached regarding the optimum dose and timing of its delivery. However, one of the studies comparing bolus versus infusion of esmolol has concluded that infusion was found more effective than bolus on controlling SAP during both intubation and sternotomy.[18] Several studies support using esmolol 2 mg/kg to effectively suppress the hemodynamic response to laryngoscopy and intubation, without any incidence of hypotension or bradycardia.[13] A study, in whom chronic β blocker therapy, was continued until the time of surgery, has concluded that esmolol did not further attenuate the HR response but did attenuate the increase in blood pressure.[18] We, therefore, used esmolol infusion in the dosage of 2 mg/kg and the results are similar to previous studies.

A study has concluded that esmolol was more effective than dexmedetomidine in the prevention of the increases in systolic, diastolic, and MAPs following endotracheal intubation. On the other hand, dexmedetomidine was more effective than esmolol in preventing the increase in HR.[12] It is of prime importance to attenuate the rise in both blood pressure and HR to prevent perioperative myocardial ischemia. We, therefore, considered that it will be appropriate to combine both dexmedetomidine and esmolol to attenuate the increase in systemic blood pressure as well as HR. It was observed that the combination of both drugs significantly decreased the HR when compared individually with dexmedetomidine and esmolol. Although all the groups suppressed blood pressure, the changes in SBP, DBP, and MAP were comparable in all the groups except at 5 min. At 5 min in esmolol group, the DBP and MAP were significantly less, inferring better control of arterial pressures by esmolol.When pulmonary artery pressures were compared, there was a significant decrease in SPAP, DPAP, and MPAP in DE group except at 3 min. This shows that the pulmonary arterial pressures were well maintained in DE group than D or E group.

The limitation of this study was the lack of a placebo group since our patients were known for coronary artery disease and it would be detrimental to produce stress in the placebo group. The plasma catecholamines levels would not be helpful to know the degree of suppression of neurohumoral pathway since etomidate was used as it is known to suppress adrenocortical axis.

We conclude that pretreatment with the combination of dexmedetomidine and esmolol infusion before induction is more effective in controlling the HR and pulmonary artery pressure. However, the combination has no additional advantage with respect to arterial blood pressure when compared to esmolol and dexmedetomidine individually in patients undergoing CABG without any untoward side effects in spite of patients being on beta blockers preoperatively.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Hamaya Y, Dohi S. Differences in cardiovascular response to airway stimulation at different sites and blockade of the responses by lidocaine. Anesthesiology 2000;93:95-103.
2. Gogus N, Akan B, Serger N, Baydar M. The comparison of the effects of dexmedetomidine, fentanyl and esmolol on prevention of hemodynamic response to intubation. Rev Bras Anestesiol 2014;64:314-9.
3. Bansal S, Pawar M. Haemodynamic responses to laryngoscopy and intubation in patients with pregnancy-induced hypertension: Effect of intravenous esmolol with or without lidocaine. Int J Obstet Anesth 2002;11:4-8.
4. Sulaiman S, Karthekeyan RB, Vakamudi M, Sundar AS, Ravullapalli H, Gandham R, *et al.* The effects of dexmedetomidine on attenuation of stress response to endotracheal intubation in patients undergoing elective off-pump coronary artery bypass grafting. Ann Card Anaesth 2012;15:39-43.
5. Menda F, Köner O, Sayin M, Türe H, Imer P, Aykaç B, *et al.* Dexmedetomidine as an adjunct to anesthetic induction to attenuate hemodynamic response to endotracheal intubation in patients undergoing fast-track CABG. Ann Card Anaesth 2010;13:16-21.
6. Hussain AM, Sultan ST. Efficacy of fentanyl and esmolol in the prevention of haemodynamic response to laryngoscopy and endotracheal intubation. J Coll Physicians Surg Pak 2005;15:454-7.
7. Keniya VM, Ladi S, Naphade R. Dexmedetomidine attenuates sympathoadrenal response to tracheal intubation and reduces perioperative anaesthetic requirement. Indian J Anaesth 2011;55:352-7.
8. Bajwa SJ, Kaur J, Singh A, Parmar S, Singh G, Kulshrestha A, *et al.* Attenuation of pressor response and dose sparing of opioids and anaesthetics with pre-operative dexmedetomidine. Indian J Anaesth 2012;56:123-8.
9. Laha A, Ghosh S, Sarkar S. Attenuation of sympathoadrenal responses and anesthetic requirement by dexmedetomidine. Anesth Essays Res 2013;7:65-70.
10. Sagiroglu AE, Celik M, Orhon Z, Yuzer S, Sen B. Different doses of dexmedetomidine on controlling hemodynamic responses to tracheal intubation. Int J Anaesth 2010;27:2.
11. Gulabani M, Gurha P, Dass P, Kulshreshtha N. Comparative analysis of efficacy of lignocaine 1.5 mg/kg and two different doses of dexmedetomidine (0.5 μg/kg and 1 μg/kg) in attenuating the hemodynamic pressure response to laryngoscopy and intubation. Anesth Essays Res 2015;9:5-14.
12. Srivastava VK, Agrawal S, Gautam SK, Ahmed M, Sharma S, Kumar R, *et al.* Comparative evaluation of esmolol and dexmedetomidine for attenuation of sympathomimetic response to laryngoscopy and intubation in neurosurgical patients. J Anaesthesiol Clin Pharmacol 2015;31:186-90.
13. Singh S, Laing EF, Owiredu WK, Singh A. Comparison of esmolol and lidocaine for attenuation of cardiovascular stress response to laryngoscopy and endotracheal intubation in a Ghanaian population. Anesth Essays Res 2013;7:83-8.
14. Venn RM, Grounds RM. Comparison between dexmedetomidine and propofol for sedation in the Intensive Care Unit: Patient and clinician perceptions. Br J Anaesth 2001;87:684-90.
15. Shrestha GS, Marhatta MN, Amatya R. Use of gabapentin, esmolol or their combination to attenuate haemodynamic response to laryngoscopy and intubation. Kathmandu Univ Med J (KUMJ) 2011;9:238-43.
16. Bensky KP, Donahue-Spencer L, Hertz GE, Anderson MT, James R. The dose-related effects of bolus esmolol on heart rate and blood pressure following laryngoscopy and intubation. AANA J 2000;68:437-42.
17. Reddy SV, Balaji D, Ahmed SN. Dexmedetomidine vs. esmolol to attenuate the hemodynamic response to laryngoscopy and tracheal intubation: A randomized double-blind clinical study. Int J Appl Basic Med Res 2014;4:95-100.
18. Efe EM, Bilgin BA, Alanoglu Z, Akbaba M, Denker C. Comparison of bolus and continuous infusion of esmolol on hemodynamic response to laryngoscopy, endotracheal intubation and sternotomy in coronary artery bypass graft. Braz J Anesthesiol 2014;64:247-52.