Comparison of oral metoprolol versus telmisartan premedication on blood loss and hypotensive anesthesia in patients treated for Orthognathic Surgery

Arvinderpal Singh[1,*], Anita Kumari[2], Ruchi Gupta[3]

[1,2]Associate Professor, [3]Professor, Sri Guru Ram Das Institute of Medical Sciences & Research, Amritsar, Punjab

***Corresponding Author:**
Email: isamdrap@yahoo.co.in

Abstract

Purpose: This study was aimed to compare blood pressure reducing effects of oral metoprolol versus telmisartan premedication as adjuvant to fentanyl and sevoflurane on various parameters of anesthesia during orthognathic surgery. Additional use of nitroglycerin (NTG) was also seen as an efficacy parameter for inducing deliberate hypotension.

Materials and Methods: Ninety patients to be operated for orthognathic surgeries were enrolled in the study and were randomly assigned to one of three groups as group A (n=30), an angiotensin receptor antagonist group, given telmisartan 40 mg orally and group B (n=30) given cardio-selective β blocker metoprolol 100 mg orally, and group C (n=30) given inactive placebo as control group. The drugs were given per orally 1 h before anesthesia induction. Inj NTG was used as an adjuvant to achieve deliberate hypotension in case mean arterial blood pressure (MAP) was not adequately controlled inspite of administering maximum dose of fentanyl and sevoflurane.

Results: The blood loss was significantly reduced in group A and group B when compared to group C. There was significant increase in over the target range of MAP percentage in group C as compared to groups A and B during deliberate hypotension (DH). The amount of NTG used was significantly lower in group A and B when compared to group C.

Conclusion: Premedication with both oral telmisartan 40 mg and metoprolol 100 mg along with fentanyl and sevoflurane anesthesia decreased blood loss. There was also achievement of satisfactory DH during orthognathic surgery with both the drugs. The outcome of anesthesia was better with telmisartan and metoprolol like reduced surgery duration, reduced duration of blood loss and reduced additional use of drugs than given only placebo group.

Keywords: Metoprolol, Telmisartan, Premedication, Blood loss, Orthognathic surgery.

Date of Acceptance: 21st March, 2017 **Date of Manuscript Receive:** 4th October, 2016

Introduction

Orthognathic surgery is maxillary surgery which attempts to correct underlying skeletal deformities, improve facial appearance and improve functions of maxilla. The blood loss during this operative procedure is commonly seen while undergoing orthognathic surgery and even may requires blood transfusion. To correct this complication controlled hypotension during a surgical procedure decreases blood pressure and subsequently to improve the surgical field.[1] However, due to presence of hard bony skeleton structure and underlying orofacial blood vessels at the incision site, orthognathic surgery is encountered with massive intra-operative bleeding which increases morbidity and mortality of patients. This also increases duration of anesthesia, intraoperative surgical complications like nerve injury, surgical site infection, fixation problems of implants, temporomandibular joint disorder, malpositioning of bony segments. The associated blood loss may be so massive that may even require blood transfusion.[2] The lowering of the patient's blood pressure or controlled hypotension in patients on orthognathic surgery has been practiced since decades.[3,4] It is basically a sort of natural survival mechanism which prevents the patients from blood loss undergoing orthognathic surgery and it also helps in patient stabilization and increases early recovery. Hypotensive anesthesia is also used in patients undergoing spinal surgery, hepatic resections, hip or knee arthroplasty, craniosynostosis, robotic surgery, and major maxillofacial operations.[5,6] Various agents like sodium nitroprusside (SNP), nitroglycerin (NTG), and inhalational anesthetics are been successfully used in patients requiring deliberate hypotension.[7] NTG is more suitable than SNP due to better benefit/risk ratio, lesser inter-individual variations in reducing bleeding after achieving adequate DH. However inhalational anesthetic drugs can achieve DH at high dose but this high concentrations of anesthetic can be hepatotoxic or nephrotoxic.[8,9] It was a randomized, double-blind, placebo-controlled study with a hypothesis that orally given telmisartan, metoprolol in combination with fentanyl under sevoflurane anesthesia, reduces blood loss during orthognathic operative procedure by achieving DH without the complications such as reflex tachycardia, excessive blood loss, enhanced surgery duration of surgery and additional requirement of drugs.

Materials and Methods

Study design: Approval was taken from the Institutional Ethics Committee before start of study. Ninety patients in age group 18-60 years were enrolled in the study and written informed consent was taken from all the patients undergoing orthognathic surgery as

per American Society of Anesthesiologists (ASA) I–II physical status criteria.[10] Patients with history of diabetes mellitus, renal artery stenosis, coronary heart diseases, heart rate <60, systolic blood pressure >140 or <100 mm Hg, hepatic failure, chronic renal failure, drug adverse reactions, disease of CNS, psychiatric illness, asthma, or patients taking treatment for systemic disease were not enrolled in the study.

Randomization: It was a double blinded study as all the investigators including anesthetist, surgeons, patients, and recovery nurses were blinded to study groups allocated the type of drugs. Using a computer-generated table for random numbers, patients were randomly assigned to one of three groups with 30 patients in each group as the angiotensin receptor antagonist group (group A) given 40 mg telmisartan, the β-blocker group (group B) given 100 mg metoprolol and the control group given inactive placebo tablet (group C). The blinding was done by putting all the tablets in a similar looking capsule and the capsules were put in separate container labeled as group A, B and C respectively. The drugs were given orally to the patients 1 h before the induction of anesthesia. Monitoring of the adverse drug effects such as vomiting, diarrhea, dry cough, bradycardia, chest pain, cardiac arrhythmia, hypotension, confusion, and hypersensitivity reactions were evaluated in pre-generated performa.[11,12]

Procedure: Patients were intravenously given 0.1 mg of glycopyrrolate as a premedication as an anti-secretory agent. Anesthesia was induced with 2 mg/kg of propofol, 0.6 mg/ kg of rocuronium, and 1 μg/kg of fentanyl followed by blood pressure regulation, electrocardiography, and measurement of oxygen saturation (SpO_2) as the patient arrived in operative room. After nasotracheal intubation, the patients' MAP (mean arterial pressure) and heart rate (HR) was monitored regularly. The mechanically ventilation with a tidal volume of 8 mL kg-1 of ideal body weight was done in patients at 50% air with oxygen. The respiratory rate of the patients was adjusted to maintain the end-tidal carbon dioxide (CO_2) tension at 35–40 mm of Hg. DH was induced to the surgeon's request after completion of the main surgical procedures. Inhalation anesthesia with sevoflurane was maintained at an age-adjusted minimal alveolar concentration of 1.0. The premedication dose of intravenous fentanyl as 50 mcg IV stat, 1 hr. prior to surgery as infusion was given and maintenance dose of 1-2 mcg/kg/hr. was maintained as an infusion.[13] Inj NTG was an adjuvant agent to achieve DH when MAP was not controlled to the desired values, inspite of the administration of the maximum fentanyl dose (2 μg/kg/hour) with sevoflurane. Additionally, the target range of MAP (percentage) during DH was also calculated, target range of MAP (percentage) for DH and hematocrit (Hct) was maintained at >27% during the surgical procedure. Intraoperative fluid required, urine output, and loss of intraoperative blood was recorded hourly. The loss of blood was estimated by measuring the amount of blood drainage in suction bottle, surgical drapes, and by comparing weigh of gauze sponges both pre and post operatively. Intraoperative fluid was given with Lactated Ringer's Solution at a constant rate of 5–10 mL/kg/ hr. If the blood loss was >300 mL, 10 % mannitol was given at a 1:1 ratio, and if Hct was <27%, a blood transfusion was started. Hypotension (MAP<60 mm Hg) was corrected using 6 mg of intravenous mephentermine. While mucosal suturing, 100 mg inj. tramadol and 4 mg of inj. ondansetron was administered to all patients intravenously for decreasing postoperative pain and as an antiemetic agent, respectively. The hemodynamics changes and any adverse effects appearing during 24 hours postoperatively were also monitored.

Statistical analysis: All the data obtained was presented as mean± SD and statistical analysis of the data was done using Student's t-test, ANOVA, Fischer's exact test, or the Wilcoxon rank sum test when appropriate. Differences were considered statistically non-significant when $P > 0.05$, S: Significant ($p<0.05$) and HS: Highly significant ($p<0.001$).

Results

Ninety patients were enrolled in the study, and two patients with prior history of cardiac surgery and hypertension were excluded and in place of these two newer patients were enrolled in study. The patients were operated for simultaneous bimaxillary orthognathic surgery, including Lefort I osteotomy and mandibular ramus osteotomy and out of these 12 patients in group A, 10 in group B, and 11 in group C underwent genioplasty. Demographic data of all the patients is shown in Table 1. There was no statistically difference in sex, age, height and body mass index (BMI), hematocrit preoperatively in all the groups. Intraoperative data of the patients is presented in Table 2. Total duration of surgery was similar in group B & A, but was significantly higher in group C. Similarly the duration of DH was higher in group C when compared to group A and B. The over target range percentage during DH was higher significantly in Group A and B when compared to group C. The under target range percentage was non-significantly lower ($p>0.05$) in group C when compared to group B & A. The amount of NTG used during DH was significantly similar in group A & B but was significantly higher in group C ($p<0.01$). The MAP of the patients in group C was significantly ($p<0.01$) lower than group A & B but was non- significantly ($p>0.05$) higher in group A when compared to group B. The number of patients given mephentermine during DH was higher in group C (26 %) than group B (16%) and group A (20%). Similarly, the number of patients having HR>100 beats/ min was higher in group C (26%) when compared with group B

(10%) and group A (16%). The number of patients having MAP <60 mm Hg was more in group C (16%) when compared with group B (10%) and group A (06%) respectively. As is evident from Table 3 that intraoperative bleeding was significantly ($p<0.01$) higher in group C but there was non-significant ($p>0.05$) difference in group B & A (Table 3). Similarly, the additional use of crystalloid, colloid and total urine output was significantly ($p<0.01$) higher in group C when compared with group B & A during the surgery. The total number of days of hospital stay in patients was significantly ($p<0.05$) higher in group C than group A & B. The number of the patients required during operative procedure blood transfusion was 4 (13%), 5 (16%) and 8 (26%) in group A, B and C respectively.

Table 1: Patient Characteristics in all the groups Preoperatively

Parameters	Group A (n=30)	Group B (n=30)	Group C (n=30)
Male	19	18*	18*
Female	11	12*	12*
Age (yrs)	35.6±0.5	34.8±3.1*	37.7±2.9*
Weight (kg)	67.5±8.9	65.4±9.7*	64.9±11.9*
Height (cm)	167.2±9.7	168.2±7.8*	169.3±7.1*
BMI (kg/m2)	21.3±2.3	20.8±2.8*	22.2±3.3*
Preoperative Hct (%)	32.96±3.5	33.08±3.1*	33.28±3.4*

BMI, body mass index; Hct, hematocrit; Group A, angiotensin converting enzyme inhibitor; Group B, β-blocker; Group C, control. Data: Mean±SD, *NS: Non significant ($p>0.05$), **S: Significant ($p<0.05$), ***HS: Highly significant ($p<0.001$).

Table 2: Intraoperative Data of the patients undergoing orthognatic surgery

Parameters	Group A (n=30)	Group B (n=30)	Group C (n=30)
Duration of surgery (min)	256.7±63	266.1±64.8*	291.0±52**
Duration of DH (min)	292.1±37.4	285.8±44.1*	201.0±54.1**
Over target range during DH (%)	18.0±10.3	20.8±7.0*	25.3±17.7**
Target range during DH (%)	60.4±10.5	62.0±12.5*	50.7±12.1**
Under target range during DH (%)	11.9±9.4	10.6±7.3*	9.4±7.5*
NTG amount used during DH (μg/kg/min)	4.2±10.7	4.8±10.9**	10.6±18.7**
MAP during intraoperative procedure (mm Hg)	72.01±18.5	68.4±11.5*	60.4±17.5**
No of Patients given mephentermine during DH	06 (20%)	05(16%)	08 (26%)
No of Patients with HR >100 (min/mt.)	05 (16%)	03 (10%)	08 (26%)
No of Patients with MAP <60 (mm Hg)	02 (6%)	03 (10%)	05 (16%)

DH, deliberate hypotension; NTG, nitroglycerin; A, angiotensin converting enzyme inhibitor; B, β-blocker; C, control. Data: Mean±SD, *NS: Non significant ($p>0.05$), **S: Significant ($p<0.05$), ***HS: Highly significant ($p<0.001$).

Table 3: Loss of Blood, additional fluid required, and urine output intraoperatively

Parameter	Group A (n=30)	Group B (n=30)	Group C (n=30)
Intraoperative bleeding (mL)	522±154.4	563±308.1*	830±355.7**
Crystalloid required (mL)	1446.5±369.8	1537.5±404.8*	1944±598.6**
Colloid required (mL)	447.8±454.0	502.1±479.9*	738.0±587.5**
Total Urine output (mL)	380.0±378.8	412.8±365*	640.4±447.1**
Duration of postoperative stay (days)	4.26±0.54	5.02±0.57*	6.86±0.70**
No of patients requiring blood transfusion	04 (13%)	05 (16%)	08 (26%)

A, angiotensin receptor antagonist converting enzyme inhibitor; B, β-blocker; C, control. Data: Mean±SD, *NS: Non significant ($p>0.05$), **S: Significant ($p<0.05$), ***HS: Highly significant ($p<0.001$).

Discussion

Orthognathic procedure being a complex surgical procedure is associated with a considerable amount of blood loss during surgery. The reason behind this is the highly vascular nature of the facial structures especially of the maxillary and mandibular structures. It is associated with significant intra-operative blood loss in majority of the patients especially seen in the beginning of the procedure while performing osteotomies. Many techniques to reduce blood loss associated with orthognathic surgery have been described and the most established, well documented is hypotensive anesthesia.[5] Sevoflurane is commonly used inhalational hypotensive anesthetic agent having vasodilatory properties as well. It is used as a singly to induce hypotension in orthognathic surgery. However, these patients are commonly given additional other hypotensive anesthetic agents along with sevoflurane.[14] Since blood transfusion is associated with various complications like transfusion-associated infections, immunological transfusion reactions and lethal mismatch transfusion.[15] Thus, the main objective of this study was to establish that preoperative treatment with a β-blocker or angiotensin 2 receptor antagonists (AT1 antagonist) can significantly reduce total blood loss during surgery by establishing controlled hypotension. However, it is common for patients to receive other hypotensive anesthetic agents in combination with sevoflurane. Multi-drug combination has additional advantage of reducing patients' mean arterial pressure and thereby reducing the complications.[16] This study establishes that during orthognathic surgery, preoperative treatment with telmisartan 40 mg and metoprolol 100 mg decreases blood loss and achieved satisfactory DH using anesthesia with fentanyl and sevoflurane. DH is used in surgeries having high blood loss and requires blood transfusion. A number of reports have established that DH decreases intraoperative blood loss.[17,18] High dose of inhalation anesthetics when used to achieve adequate hypotension are associated with liver or kidney toxicity so vasodilator, such NTG, is most commonly employed hypotensive agents. However, NTG can produce direct vasodilation and also reduces the preload via venodilation. Peripheral vasodilatation due NTG can result in reflex baroreceptor stimulation producing reflex tachycardia and increase in myocardial contractility. Consequently the stimulation of sympathetic and renin-angiotensin systems is responsible for the rebound hypertension which leads to an increase in surgical tissue injury, blood loss, and also affect level and duration of hypotension.[19] Telmisartan is AT (angiotensin) type 1 receptor antagonist (ARB) and its role is well established for the treatment of hypertension, CHF, diabetic nephropathy. Telmisartan is unique in the class of ARBs as is associated with high affinity for the angiotensin II type 1 receptor binding with a long duration action, highly lipophilic and has a long plasma half-life.[20] Telmisartan has significant protective effects against tissue remodeling, along with equipotent blood pressure lowering effects, compared to other RAS inhibitors, captopril or losartan.[21] Metoprolol a cardioselective β1-adrenergic receptor blocking agent is clinically used in acute myocardial infarction (MI), heart failure, ischemic cardiac disease and mild to moderate hypertension.[22] Oral pretreatment with metoprolol given prior to surgery has been shown to decrease blood loss during surgery via decreasing HR, blood pressure, and cardiac output. This increases the operative field in surgery decreases duration of surgery and hence lessens post-surgical morbidity.[23] Thus the present study concluded that the duration of surgery and DH was favorably lower in patients preoperatively given telmisartan and metoprolol. However, telmisartan was shown to have better effects in such patients than metoprolol. Kim et al[24] have shown that oral ACE inhibitor when given preoperatively in patients undergoing orthognathic surgery showed a lesser blood loss significantly, and over the target range of MAP (percentage) during DH was significantly higher. Similarly, Ghosh et al[25] in 90 adult patients has shown that metoprolol 100 mg, decreased the hemodynamic response favorably in patients undergoing peripheral nerve injury repair and also required lower dose of propofol. NTG was infused when the target range blood pressure was not achieved while using anesthetic agents alone. NTG is a potent venodilator that decreases the venous return, cardiac output and fall in blood pressure. However; an excessive drop in blood pressure can occur in patients with a low blood volume which can compromise coronary blood flow precipitating angina like episodes in patients with ischemic cardiac disease. Telmisartan group required to achieve adequate DH significantly lowers dose of NTG and has a favorable clinical significance, as is associated with lower intraoperative blood loss, lower NTG requirement and thus a reduction in associated adverse effects of NTG. The percentage of patients given mephentermine during DH among the three groups was slightly higher in placebo group signifying that telmisartan and metoprolol was more effective to achieve deliberate hypotension and also in reducing the amount of NTG as an adjuvant agent during surgery as compared to placebo. In clinical practice various combinations of inhalation anesthetics are used in general anesthesia to induce DH[26] but most of these inhalation agents produce vasodilation in a dose dependent manner with increased intraoperative blood. The renin-angiotensin system (RAS) is important in regulation of arterial tone and cardiac functions. Angiotensin II iproduces vasoconstriction and has been shown to be responsible for vascular wall thickening via non-hemodynamic mechanisms such as proliferation or overgrowth of vascular smooth muscle, elastin and collagen fibers.[27] Perioperative hemorrhage is an important concern during orthognathic surgery as

may even require blood transfusions. The result of previous studies have established that pretreatment with a β-blocker is associated with benefits during DH for the reduction of reflex tachycardia and rebound hypertension.[28] The possible explanation seems to be that premedicated metoprolol is associated with blockage of Beta-1 receptors in heart which consequently leads to decrease in heart rate and force of contraction which is associated with lower blood loss. Duration of DH and surgery was significantly longer in telmisartan than placebo group in the present study. The cause may be that DH was controlled in patients given telmisartan and metoprolol. This indirectly indicates that duration of surgery during DH was increased in placebo group due to the lower quality of the operative field in placebo group. No untoward hemodynamic instability was noted in all the patients given metoprolol, telmisartan and placebo respectively. In the placebo group, the MAPs was significantly lower than in patients given telmisartan and metoprolol. However, there was no statistical difference in the frequency of hypotension after induction of anesthesia in telmisartan and metoprolol group; however a non-significant ($p>0.05$) increase in MAP was seen in telmisartan group. Thus, it infers that telmisartan is a better agent than metoprolol to stabilize MAP when given preoperatively, even after the end of DH. Acute elevation of MAP at the end of DH may increase the risk of re-bleeding. Thus stabilization of MAP post-DH is beneficial in such patients. Intraoperative blood loss was significantly lower in telmisartan treated patients when compared to placebo group; however metoprolol treated patients showed a non-significant ($p>0.05$) higher blood loss than telmisartan group. Thus it can be concluded that premedication with oral telmisartan under general anesthesia attenuate blood loss during orthognathic surgery more effectively than metoprolol. Since no such comparison is available in patients undergoing orthognathic surgery in literature, so we propose that the effective use of oral telmisartan to induce DH in patients undergoing orthognathic surgeries. No prior studies have established the impact of a preoperative oral β-blocker or AT1 receptor antagonist administration on adequate DH, intraoperative blood loss and MAP so the findings of this study will help in establishing the role of telmisartan in patients undergoing orthognathic surgery.

Conclusion

The present study concludes that premedication with telmisartan and metoprolol significantly reduces intraoperative blood loss with satisfactory DH in patients undergoing orthognathic surgery with fentanyl and sevoflurane. However, telmisartan was marginally more effective in such patients in such patients and is a safer alternative in patients having coexisting problems like asthma, conduction defects, and uncontrolled diabetes.

Acknowledgement

We would also like to show our gratitude to Dr Rahat Kumar, Professor Pharmacology, SGRD Institute of Medical Sciences and Research, Amritsar for sharing his pearls of wisdom with us during the course of this research work. His guidance helped us in all the time of research and writing of this research article.

References

1. Mohammadi F, Marashi M, Tavakoli I, Khakbaz O. Effects of oral clonidine premedication on hemodynamic status in bimaxillary orthognathic surgery: A double-blind randomized clinical trial. J Craniomaxillofac Surg. 2016 Apr;44(4):436-9.
2. Carlos E, Monnazzi MS, Castiglia YM, Gabrielli MF, Passeri LA, Guimarães NC. Orthognathic surgery with or without induced hypotension. Int J Oral Maxillofac Surg 2014;43:577-80.
3. Mostert JW. "Safe hypotensive anesthesia." The Journal of the American Medical Association 1973;225(1):64–5.
4. Sataloff RT, Brown ACD, Sheets EE, and Rubinstein MI. A controlled study of hypotensive anesthesia in head and neck surgery. Ear, Nose and Throat Journal. 1987;66(12):479–85.
5. Pi˜neiro-Aguilar A, Somoza-Martin M, Gandara-Rey JM, and Garc´ıa-Garc´ıa A. Blood loss in orthognathic surgery: a systematic review. Journal of Oral and Maxillofacial Surgery. 2011;69(3):885–92.
6. Chen CM, Lai SS, Hsu KJ, Lee HE, and Huang HL. Assessment of the related factors of blood loss and blood ingredients among patients under hypotensive anesthesia in orthognathic surgery. Journal of Craniofacial Surgery. 2011;22(5):1594–7.
7. Degoute CS. Controlled hypotension: a guide to drug choice. Drugs 2007;67:1053-76.
8. Testa LD, Tobias JD. Pharmacologic drugs for controlled hypotension. J Clin Anesth 1995;7:326-37.
9. Boezaart AP, van der Merwe J, Coetzee A. Comparison of sodium nitroprusside and esmolol induced controlled hypotension for functional endoscopic sinus surgery. Can J Anaesth 1995;42(5):373-6.
10. Dripps RD. New classification of physical status. Anesthesiol 1963;24:111.
11. He YM, Feng L, Huo DM, Yang ZH, Liao YH. Enalapril versus losartan for adults with chronic kidney disease: a systematic review and meta-analysis. Nephrology (Carlton) 2013;18:605-14.
12. Amr YM, Amin SM. Effects of preoperative β-blocker on blood loss and blood transfusion during spinal surgeries with sodium nitroprusside-controlled hypotension. Saudi J Anaesth 2012;6:263-7.
13. Lessard MR, Trépanier CA, Baribault JP, Brochu JG, Brousseau CA, Coté JJ et al. Isoflurane-induced hypotension in orthognathic surgery. Anesth Analg 1989;69:379-83.
14. Jeong J, Portnof JE, Kalayeh M, Hardigan P. Hypotensive anesthesia: Comparing the effects of different drug combinations on mean arterial pressure, estimated blood loss, and surgery time in orthognathic surgery. Craniomaxillofac Surg. 2016 Jul;44(7):854-8.
15. Kleinman S, Chan P, Robillard P. Risks associated with transfusion of cellular blood components in Canada. Transfus Med Rev. 2003 Apr;17(2):120-62.
16. Jeong J1, Portnof JE, Kalayeh M, Hardigan P. Hypotensive anesthesia: comparing the effects of different drug combinations on mean arterial pressure,

estimated blood loss, and surgery time in orthognathic surgery. J Craniomaxillofac Surg. 2016 Jul;44(7):854-8.
17. Precious DS, Splinter W, Bosco D. Induced hypotensive anesthesia for adolescent orthognathic surgery patients. J Oral Maxillofac Surg. 1996;54:680-3.
18. Schaberg SJ, Kelly JF, Terry BC, Posner MA, Anderson EF. Blood loss and hypotensive anesthesia in oral-facial corrective surgery. J Oral Surg. 1976;34:147-56.
19. Yoshikawa F, Kohase H, Umino M, Fukayama H. Blood loss and endocrine responses in hypotensive anaesthesia with sodium nitroprusside and nitroglycerin for mandibular osteotomy. Int J Oral Maxillofac Surg. 2009;38:1159-64.
20. Sharpe M, Jarvis B, Goa KL. Telmisartan: a review of its use in hypertension. Drugs. 2001;61(10):1501-29.
21. Wagner J, Drab M, Bohlender J, Amann K, Wienen W, Ganten D. Effects of AT1 receptor blockade on blood pressure and the renin-angiotensin system in spontaneously hypertensive rats of the stroke prone strain. Clin Exp Hypertens. 1998;20:205–21.
22. Benfield P, Clissold SP, Brogden RN. Metoprolol: An updated review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy, in hypertension, ischaemic heart disease and related cardiovascular disorders. Drugs. 1986 May;31(5):376-429.
23. Nair S, Collins M, Hung P, Rees G, Close D, Wormald PJ. The effect of beta-blocker premedication on the surgical field during endoscopic sinus surgery. Laryngoscope. 2004 Jun;114(6):1042-6.
24. Kim NY, Yoo YC, Chun DH, Lee HM, Jung YS, Bai SJ. The Effects of Oral Atenolol or Enalapril Premedication on Blood Loss and Hypotensive Anesthesia in Orthognathic Surgery. Yonsei Med J. 2015 Jul;56(4):1114-21.
25. Ghosh I, Bithal PK, Dash HH, Chaturvedi A, Prabhakar H. Both clonidine and metoprolol modify anesthetic depth indicators and reduce intraoperative propofol requirement. J Anesth. 2008;22(2):131-4.
26. Shin S, Lee JW, Kim SH, Jung YS, Oh YJ. Heart rate variability dynamics during controlled hypotension with nicardipine, remifentanil and dexmedetomidine. Acta Anaesthesiol Scand 2014;58:168-76.
27. Dzau VJ, Gibbons GH, Pratt RE. Molecular mechanisms of vascular renin-angiotensin system in myointimal hyperplasia. Hypertension. 1991 Oct; 18(4 Suppl):II100-5.
28. Marshall WK, Bedford RF, Arnold WP, Miller ED, Longnecker DE, Sussman MD et al. Effects of propranolol on the cardiovascular and renin-angiotensin systems during hypotension produced by sodium nitroprusside in humans. Anesthesiology. 1981;55:277-80.