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Research article

Controlled hypotensive anesthesia for endoscopic endonasal repair of cerebrospinal fluid rhinorrhea: A comparison between clevidipine and esmolol: Randomized controlled study

Essam F. Abdelgalel

Department of Anesthesia and Surgical Intensive Care, Faculty of Medicine, Zagazig University, Zagazig, Egypt

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ABSTRACT

Background: The aim of this study was to evaluate the efficacy of intravenous infusion of clevidipine or esmolol for producing controlled hypotension during endoscopic repair of cerebrospinal fluid (CSF) rhinorrhea.

Patients and methods: Fifty adult ASA I and II patients scheduled for endoscopic repair of CSF rhinorrhea were randomized into one of two groups. Group C (25 patients) received clevidipine 0.5 mcg/kg/min increased by 0.5 mcg/kg/min every 3–5 min to achieve the target mean arterial pressure (MAP) of 55–65 mmHg. Group E (25 patients) received esmolol infusion 50 mcg/kg/min increased by 50 mcg/kg/min every 3–5 min to achieve the target MAP. Surgical field Quality, blood loss, haemodynamic parameters, surgeons' satisfaction and adverse events were recorded.

Results: Time to reach target MAP was significantly shorter in group C compared to group E. Number of patients needed nitroglycerine was significantly higher in group E compared to group C (8 versus 2 respectively). The nitroglycerine dose needed/patient in group E was significantly more compared to group C. Surgeon satisfaction score was significantly higher in group C compared to group E. More patients in group E developed bradycardia compared to group C. Mean arterial pressure was significantly lower in group C compared to group E after 5 and 10 min from the start of the studied drugs infusion while it was significantly higher in group C after 25 min from the start of the studied drugs. The heart rate (HR) was significantly lower in group E compared to group C 10 min after starting drugs infusion till the end of surgery.

Conclusion: Both clevidipine and esmolol are effective for inducing controlled hypotension during endoscopic repair of CSF rhinorrhea. Clevidipine has the advantage of having shorter time to reach target MAP with less need of additional hypotensive agent and better surgeon satisfaction.

1. Introduction

Cerebrospinal fluid (CSF) rhinorrhea may be spontaneous or secondary to head injury, surgery, neoplastic invasion of the skull base or congenital malformations [1]. Endoscopic endonasal repair has become the surgical approach of choice for CSF leak as it is safe and less invasive with a high success rate [2,3].

Controlled hypotension during surgery allows better surgical field visibility with decreased blood loss, surgery duration and lower incidence of complications [4]. A lot of medications can be used for controlled hypotensive anesthesia. The ideal drug for controlled hypotension should be easily administered with dose-dependent effects, fast onset and short term effect without toxic metabolites and minimal adverse effects [5].

Clevidipine is an intravenous calcium channel antagonist that can rapidly control blood pressure by direct arterial vasodilatation [6–9]. It has a short half-life approximately one to three minutes due to rapid metabolism by blood and tissue esterases [10,11].

Esmolol is an ultrashort selective β1-adrenoreceptor blocker which has short elimination half-life with rapid clearance and can be used for controlled hypotension without reflex tachycardia [12,13].

The primary outcome of this study was to compare the efficacy of intravenous infusion of clevidipine and esmolol for producing controlled hypotension during endoscopic repair of CSF rhinorrhea. The secondary outcome was to compare between the two drugs regarding quality of surgical field, surgeons' satisfaction and adverse events.

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E-mail address: essamfathi1968@yahoo.com.

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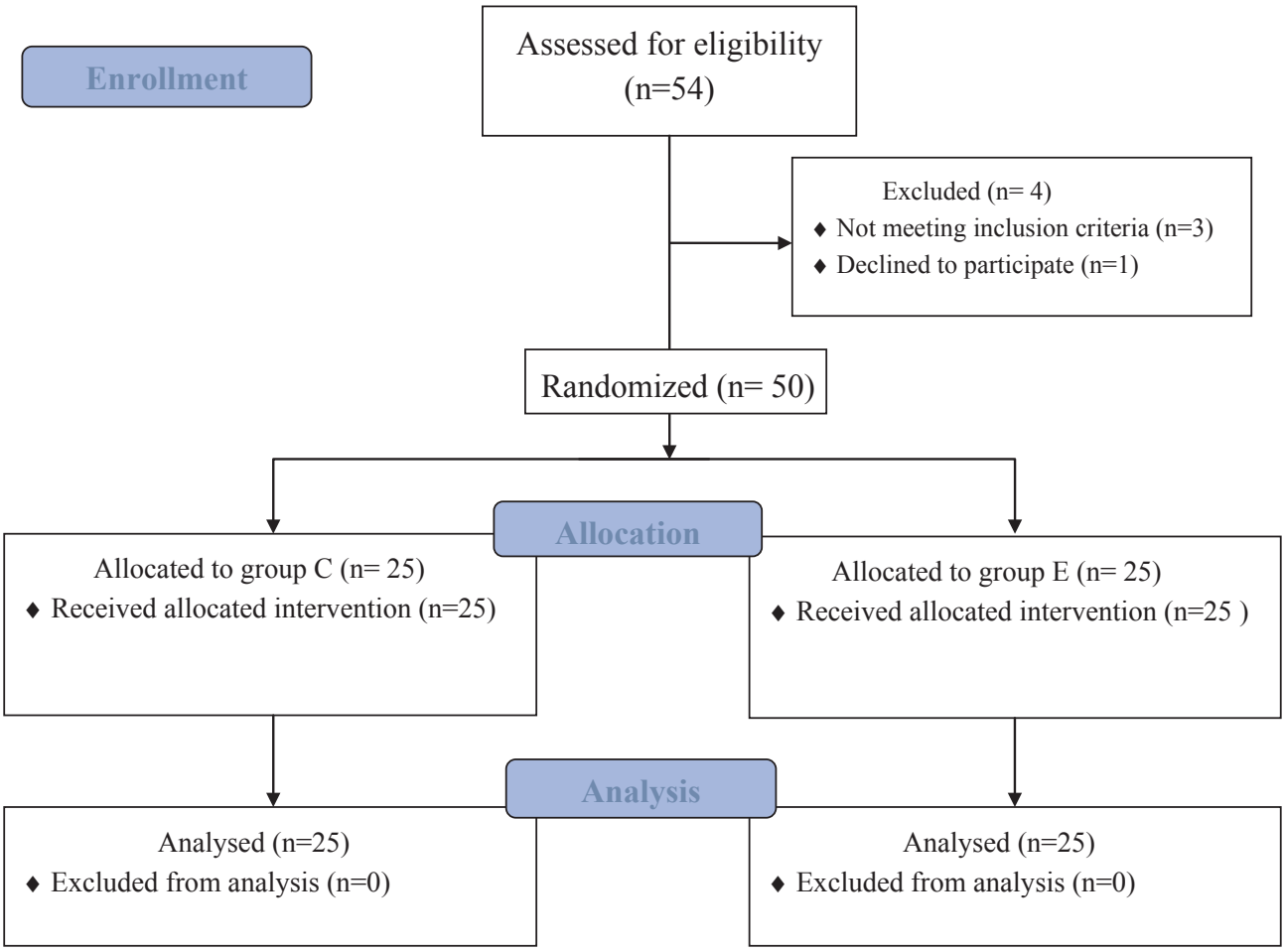

Fig. 1. Patient's flowchart demonstrating the number of patients eligible for inclusion into the study, enrollment, randomization and analysis.

2. Patients and methods

2.1. Study design

This prospective, randomized double-blinded study was carried out in zagazig university hospital from January 2014 to August 2017 after our institutional review board approval and obtaining a written informed consent from all patients. Fifty adult ASA physical status I and II patients planned for endoscopic repair of CSF rhinorrhea under general anesthesia were randomly allocated to either clevidipine group (group C) or esmolol group (group E) (Fig. 1). Randomization was done using block randomization with block size of 6 and allocation ratio of 1:1 and sealed envelopes were used for allocation concealment. Patients with cardiovascular disease (hypertension, heart block, severe aortic stenosis, heart failure, arrhythmia or coronary artery disease), cerebrovascular insufficiency, coagulation disorders, renal or hepatic insufficiency, a known or suspected allergy to the study drugs or its components, or patients with disorders in lipid metabolism, were excluded from the study.

After proper preanesthesia evaluation two eighteen gauge intravenous cannulas were inserted and all patients were monitored by pulse oximetry, ECG and non-invasive blood pressure and baseline measurements were measured and recorded.

Midazolam 0.05 mg/kg was given intravenously and patients were placed in the sitting position and lumber puncture was done under complete aseptic precautions at L_3-L_4 or L_4-L_5 interspace via a midline approach using g 22 spinal needles.0.25 ml of a 10% sterile fluorescein dye was mixed with the aspirated CSF (total 10 ml) then reinjected slowly into the subarachnoid space. Patients were turned to Trendelenburg position for 20–30 min. Preoxygenation for 3 min then general anesthesia was induced with propofol 2 mg/kg, fentanyl 2 mcg/kg and rocuronium 0.6 mg/kg. Oral endotracheal intubation with cuffed endotracheal tube and oropharyngeal pack was inserted then mechanical ventilation was started to keep the $_{ET}CO_2$ 30–35 mmHg. Anesthesia was maintained using isoflurane 1–2%. All patients were monitored for Invasive arterial blood pressure via radial artery, oxygen saturation, ECG, temperature and Capnography.

Patients were put supine with head up 15–20°. Cotton soaked with a solution containing lignocaine 2% and epinephrine 1/10,000 was applied to nasal mucosa for 5 min.

Group C (25 patients) received clevidipine (cleviprex, Fresenius Kabi, Austria) (0.5 mg/ml) which was started at 0.5 mcg/kg/min and increased in increments of 0.5 mcg/kg/min every 3–5 min to a maximum of 8 mcg/kg/min to achieve the target mean arterial pressure (MAP) (55–65 mmHg).

Group E (25 patients) received esmolol (Baxter healthcare corporation, USA) (10 mg/ml) infusion started at 50 mcg/kg/min which was increased by 50 mcg/kg/min every 3–5 min if needed to achieve the target MAP with a maximum infusion rate of 300 mcg/kg/min. In both groups, if target MAP was not attained with the maximum dose of the studied drug, additional doses of fentanyl (0.5 mcg/kg) were given and if still not attained nitroglycerin infusion was started. Nitroglycerine was started in a dose of 0.5 μg/kg/min and increased gradually until the target MAP was achieved.

Hypotension was diagnosed if the MAP dropped below 55 mmHg and intravenous fluids were infused rapidly and the studied drug infusion was titrated down until temporarily stopped. If the MAP was still below 55 mmHg, ephedrine 6 mg was given intravenously and repeated

Table 1
Quality of surgical field (average category scale for assessment of surgical field (adapted from Fromme et al. [14]).

Grade	Surgical field assessment
0	No bleeding
1	Slight bleeding: no suctioning needed
2	Slight bleeding: required occasional suctioning
3	Slight bleeding: frequent suctioning required; bleeding threatens surgical field several seconds after suction is removed
4	Moderate bleeding: required frequent suctioning; bleeding threatens surgical field directly after suction is removed
5	Severe bleeding: constant suctioning required; bleeding appears faster than can be removed by suction; surgical field is severely threatened and surgery is usually not possible

after 3 min if needed. Tachycardia was diagnosed if heart rate increased above 100 beats/minute and propranolol 0.5–1 mg was given slowly over one minute if heart rate was more than 110 beats/minute. Bradycardia was diagnosed if heart rate decreased below 60 beats/minute and atropine 0.01 mg/kg was given if HR decreased below 50 beats/minute.

The quality of the surgical field was estimated by the surgeon every 15 min during surgery according to average category scale (ACS) [14] (Table1). The ideal average category scale was detected to be one and two. Surgeon satisfaction score was recorded. Total blood loss at the end of surgery was measured as that collected from the suction unit and by weighting the nasal swabs.

Ten minutes before the end of surgery, the study drug was stopped and reversal of neuromuscular blockade was done using neostigmine (0.05 mg/kg) and atropine (0.01 mg/kg). Patients were extubated and shifted to post anesthesia care unit (PACU) for monitoring and any adverse events were noted and recorded.

For proper blindness of the study and because clevidipine is a white solution while esmolol is a clear solution, all patients in both groups received two syringe pumps infusions via two different intravenous lines. All medications were prepared and labeled by pharmacist in 50 ml syringes. Group C patients received one syringe containing clevidipine (white color) and another syringe containing normal saline (clear) as placebo while group E patients received one syringe containing esmolol (clear) and another syringe containing intralipid 10% solution (white color) as placebo. The anesthetist was blind about the syringes contents and was dealing with both syringes as if they contain the studied drugs and was changing the rate of infusion of both syringes depending on body weight to achieve the target MAP according to the study protocol. Clevidipine syringe contains clevidipine 0.5 mg/ml while esmolol syringe contains esmolol 10 mg/ml. According to the study protocol, clevidipine was started at 0.5 mcg/kg/min and increased in increments of 0.5 mcg/kg/min every 3–5 min while esmolol started at 50 mcg/kg/min which was increased by 50 mcg/kg/min every 3–5 min. So, for any change in the rate of infusion of the syringe containing white solutions (clevidipine or intralipid) the rate of infusion of the syringe containing clear solutions (esmolol or saline) should be changed by 5 folds and vice versa.

Duration of surgery (time from application of local anesthetic soaked cotton till the surgeon puts the nasal packs at the end of surgery), duration of anesthesia (time from induction of general anesthesia till the time of extubation), duration of controlled hypotension (time from start of the studied drugs infusion till these drugs were stopped) and time to reach target MAP (time from starting the studied drugs infusion till the MAP reached 55–65 mmHg) and the medications needed (fentanyl, nitroglycerine, atropine, propranolol and ephedrine) were recorded.

2.2. Sample size calculation

Because there was no available data in the literature a pilot study was done before starting this study. Power analysis was performed using Student's *t*-test for independent samples on mean time to reach target MAP because it was the main outcome variable in the present study. The results of the pilot study showed that it was 8.3 ± 2.1 with clevidipine administration and 11.7 ± 4.9 with esmolol administration. Taking power 0.8 and alpha error 0.05, a minimum sample size of 22 patients was calculated for each group. Twenty-five patients were included for each group to compensate for possible dropouts. (MedCalc 13 for windows, MedCalc Software bvba, Ostend, Belgium).

2.3. Statistical analysis

Categorical variables were expressed as a number (percentage) and Continuous variables were expressed as mean ± SD. Continuous variables were checked for normality by using Shapiro-Wilk test. Independent samples Student's *t*-test was used to compare two groups of normally distributed data. Percent of categorical variables were compared using Chi-square test. All tests were two sided. $P < .05$ was considered statistically significant. All data were analyzed using Statistical Package for Social Science for windows version 20.0 (SPSS Inc., Chicago, IL, USA) & MedCalc for windows version 13 (MedCalc Software bvba, Ostend, Belgium) and graphically presented using Microsoft Office Excel 2010 for windows (Microsoft Cor., Redmond, WA, USA).

3. Results

Patients characteristics and baseline data were comparable in both studied groups ($p > .05$) (Table2).

Average category scale (ACS) was used to assess the surgical field quality every fifteen minutes. Table 3 shows the ACS which represents the average of all the observations recorded during the surgery. No patients in both groups had ACS grade 0. Eleven patients (44%) had ACS grade 1 in group C compared to 7 patients (28%) in group E. Average category scale was grade 2 in nine patients (36%) in group C compared to 8 patients (32%) in group E. Four patients (16%) in group C were grade 3 compared to 8 patients (32%) in group E. Only one patient (4%) was grade 4 in group C compared to 2 patients (8%) in group E. No patients had ACS grade 5 in both groups (Table3).

Duration of surgery, duration of anesthesia and duration of controlled hypotension were comparable in both groups ($p > .05$). Time

Table 2
Comparison between the studied groups as regard patients characteristics and baseline data (N = 25).

	Group C	Group E	p-Value
Age (years)	35.20 ± 16.10	33.90 ± 15.30	.770*
Gender			
Male: No. (%)	21 (84%)	19 (76%)	.480§
Female: No. (%)	4 (16%)	6 (24%)	
Body mass index (kg/m^2)	23.30 ± 7.30	21.90 ± 6.90	.487*
ASA physical status			
ASA I: No. (%)	6 (24%)	8 (32%)	.529§
ASA II: No. (%)	19 (76%)	17 (68%)	
Etiology of CSF rhinorrhea			
Spontaneous: No. (%)	14 (56%)	16 (64%)	.564§
Secondary: No. (%)	11 (44%)	9 (36%)	
Baseline parameters			
MAP (mmHg)	84.60 ± 7.20	82.90 ± 6.60	.386*
HR (beats/minute)	83.30 ± 18.50	85.10 ± 17.90	.727*
Oxygen saturation (%)	98.40 ± 1.30	97.60 ± 1.60	.055*

N = Total number of patients in each group; Quantitative data were expressed as the mean ± SD; Qualitative data were expressed as a number (%).
MAP = Mean arterial pressure. HR = Heart rate.
* Independent samples Student's *t*-test;
§ Chi-square test; $p < .05$ is significant.

Table 3
Average Category Scale (ACS) (N = 25).

Average Category Scale	Group C		Group E		p-value
Grade 0	0	(0%)	0	(0%)	.455[§]
Grade 1	11	(44%)	7	(28%)	
Grade 2	9	(36%)	8	(32%)	
Grade 3	4	(16%)	8	(32%)	
Grade 4	1	(4%)	2	(8%)	
Grade 5	0	(0%)	0	(0%)	

N = Total number of patients in each group; Qualitative data were expressed as a number (percentage).
This ACS represents the average of all recorded observations.
[§] Chi-square test; $p < .05$ is significant.

to reach target MAP was significantly shorter in group C (6.80 ± 3.10 min) compared to group E (13.90 ± 6.70 min). No significant difference between the two groups regarding the dose of intraoperative fentanyl needed (72.20 ± 25.40 μg and 79.90 ± 28.10 μg in groups C and E respectively). Number of patients needed nitroglycerine was significantly higher ($p < .05$) in group E compared to group C (8 versus 2 respectively). Also the nitroglycerine dose needed/patient in group E was significantly more (3.79 ± 0.95 mg) compared to group C (1.42 ± 0.28 mg). More patients in group E needed atropine compared to group C (4 versus 0 respectively). No patients needed propranolol in both groups while 2 patients in each group required ephedrine (Table4).

Total blood loss was slightly less in group C (177.20 ± 43.20 ml) in group C compared to group E (186.30 ± 39.80 ml) but it was statistically insignificant. Surgeon satisfaction score was significantly higher in group C compared to group E (Table 5)

More patients in group E (6 patients) developed bradycardia compared to group C (no patients) which was statistically significant. There was no significant difference among the two groups in the number of patients regarding the other adverse events (tachycardia, hypotension, nausea, vomiting and shivering) (Table 6).

Mean arterial pressure (MAP) was significantly lower in group C compared to group E after 5 and10 min from the start of the studied drugs infusion while it was significantly higher in group C after 25 min from the start of the studied drugs infusion. There was no statistically significant difference between the two groups in MAP at all the other measurements (Fig. 2)

The heart rate (HR) was significantly lower in group E compared to group C 10 min after starting infusion of the studied drugs till the end of surgery (Fig. 3).

Table 5
Total amount of blood loss, surgeons' satisfaction (N = 25).

	Group C		Group E		p-Value
Total blood loss (ml)	177.20 ± 43.20		186.30 ± 39.80		.440[*]
Surgeon satisfaction score					
Excellent	17	(68%)	8	(32%)	.049[§]
Good	5	(20%)	7	(28%)	
Fair	3	(12%)	8	(32%)	
Poor	0	(0%)	2	(8%)	

N = Total number of patients in each group; Quantitative data were expressed as the mean ± SD; Qualitative data were expressed as a number (%).
$p < .05$ is significant.
[*] Independent samples Student's *t*-test.
[§] Chi-square test.

Table 6
Adverse effects (N = 25).

	Group C		Group E		p-value
Intraoperative bradycardia	0	(0%)	6	(24%)	.022[§]
Intraoperative tachycardia	0	(0%)	0	(0%)	1.000[§]
Intraoperative hypotension	3	(12%)	4	(16%)	1.000[§]
Postoperative nausea	2	(8%)	2	(8%)	1.000[§]
Postoperative vomiting	0	(0%)	1	(4%)	1.000[§]
Postoperative shivering	6	(24%)	5	(20%)	.733[§]

N = Total number of patients in each group; Qualitative data were expressed as a number (%).
$p < .05$ is significant. These data represents the number (%) of patients who had the complication.
[§] Chi-square test.

4. Discussion

Controlled hypotensive anesthesia is usually required for optimizing the surgical field during endoscopic repair of CSF rhinorrhea.

The primary outcome of the current study was to compare the efficacy of clevidipine and esmolol for producing controlled hypotension during endoscopic repair of CSF rhinorrhea. The parameters studied to determine the efficacy were time to reach the target MAP, need for and dose of additional hypotensive agent, quality of surgical field, amount of blood loss and surgeons satisfaction. No previous studies about using clevidipine for controlled hypotension during endoscopic repair of CSF rhinorrhea or to compare it with esmolol. Clevidipine was used for hypertensive emergencies [15–17] and perioperative blood pressure control [18,19] and studied for controlled hypotension in spine surgery [20,21].

Table 4
Operative data (N = 25).

Operative data	Group C		Group E		p-Value
Duration of surgery (min)	200.50 ± 26.50		206.20 ± 24.10		.428[*]
Duration of anesthesia (min)	213.20 ± 27.20		219.90 ± 23.80		.356[*]
Duration of controlled hypotension (min)	187.40 ± 20.60		192.20 ± 17.90		.381[*]
Time to reach target MAP (min)	6.80 ± 3.10		13.90 ± 6.70		< .001[*]
Dose of intraoperative fentanyl (μg)	72.20 ± 25.40		79.90 ± 28.10		.312[*]
Patients needed nitroglycerine: No. (%)	2	(8%)	8	(32%)	.034[§]
Nitroglycerine used/patient (mg)	1.42 ± 0.28		3.79 ± 0.95		< .001[*]
Patients needed atropine: No. (%)	0	(0%)	4	(16%)	.110[§]
Patients needed propranolol: No. (%)	0	(0%)	0	(0%)	1.000[§]
Patients needed ephedrine: No. (%)	2	(8%)	2	(8%)	1.000[§]

N = Total number of patients in each group; Quantitative data were expressed as the mean ± SD; Qualitative data were expressed as a number (%).
$p < .05$ is significant. MAP = Mean arterial pressure.
[*] Independent samples Student's *t*-test.
[§] Chi-square test.

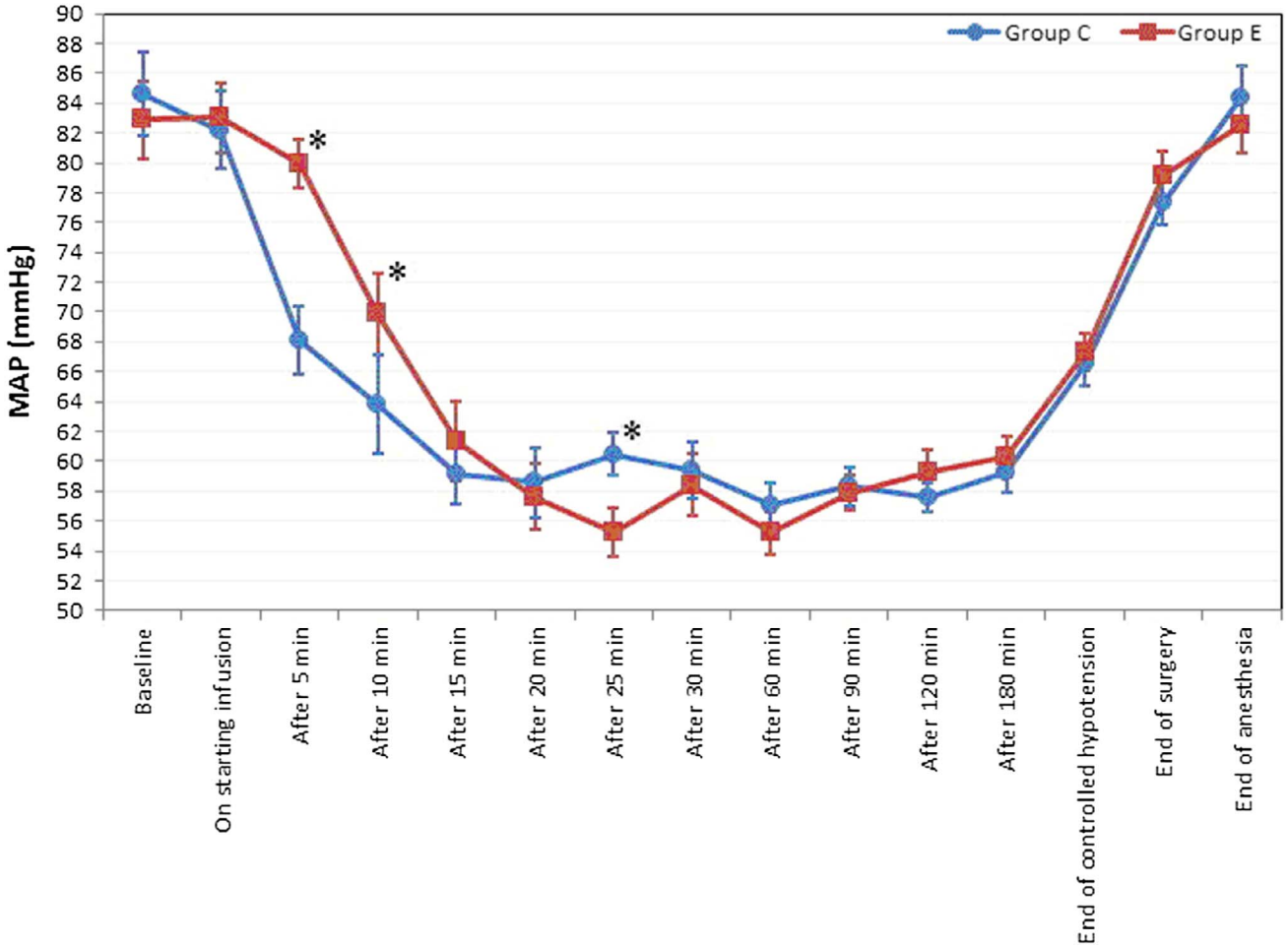

Fig. 2. Marker & error bar chart shows MAP (mmHg) at various times of measurements of the studied groups; markers represent mean; Y-error bar represent 95%confidence interval of mean, * indicate significant difference between the studied groups.

In the current study the time to reach target MAP was significantly longer in esmolol group compared to clevidipine group. This can be attributed to the direct arterial vasodilatation mediated by clevidipine [6] while esmolol mediated hypotension is secondary to its negative inotropic and chronotropic action which takes longer time. Graffagnino et al. found that the median time needed to get the target systolic blood pressure with clevidipine in patients with intracerebral hemorrhage was 5.5 min [16]. Kako et al. found that 16 out of 30 patients reached the target MAP within 5 min when clevidipine was used during posterior spine fusion in pediatric [20]. Clevidipine was started at 0.25 to 1 mcg/kg/min and increased by 0.25–1 mcg/kg/min every 3–5 min till the target MAP was reached.

In the current study, the number of patients needed nitroglycerine was significantly less in clevidipine group compared to esmolol group. Also the nitroglycerine dose needed/patient in group E was significantly more compared to group C. Das et al. [22] found that a significantly more number of patients and higher nitroglycerine dose was needed with esmolol compared to dexmedetomidine for controlled hypotension in functional endoscopic sinus surgery. More patients in esmolol group developed bradycardia compared to clevidipine group. Although the decrease in heart rate due to the negative chronotropic effect of esmolol is beneficial for controlled hypotension but 6 out of 30 patients developed bradycardia and 4 of them received atropine. The heart rate was significantly lower in esmolol group compared to clevidipine group starting after 10 min from the beginning of drugs infusion till the end of surgery.

Clevidipine as a calcium channel blocker can cause tachycardia which may be due to vasodilatation and drop of blood pressure. A nonsignificant increase in heart rate occurred after starting clevidipine infusion and the heart rate remained in sinus rhythm with no need for intervension. In a previous study by Kako et al. [20], they noticed a slight increase in heart rate of about 3 beats per minute after the initiation of the clevidipine infusion during controlled hypotension for posterior spine fusion. In agreement to our results Croft and Probst [23] found a modest increase in heart rate with no need for treatment during use of clevidipine for induced hypotension for Maxillary osteotomy.

Merry et al. [18] found that heart rate was lower during clevidipine administration compared to nitroglycerine during CABG surgery. Another study compared clevidipine with sodium nitroprusside for control of postoperative hypertension after CABG surgery showed a significant increase in heart rate with SNP compared with clevidipine [19]. In a retrospective study by Tobias [21] on using clevidipine for controlled hypotension for spine surgery 3 out of 20 patients had tachycardia that required metoprolol to control heart rate. Unlike the current study he used total intravenous anesthesia and all patients were adolescents with increasing the dose of clevidipine every 2–3 min to maintain MAP at 50–65 mmHg.

In the current study both clevidipine and esmolol were effective to get the target mean arterial pressure (MAP). But the MAP was significantly lower in clevidipine group after 5 and 10 min from the start of infusion of the studied drugs and this can be explained by the shorter time to reach target MAP with clevidipine due to the fast direct arterial vasodilatation. Also, the additional drugs (fentanyl and nitroglycerine) were started only after failure to attain the target MAP with the maximum doses of the studied drugs.

Although average category scale and total blood loss were

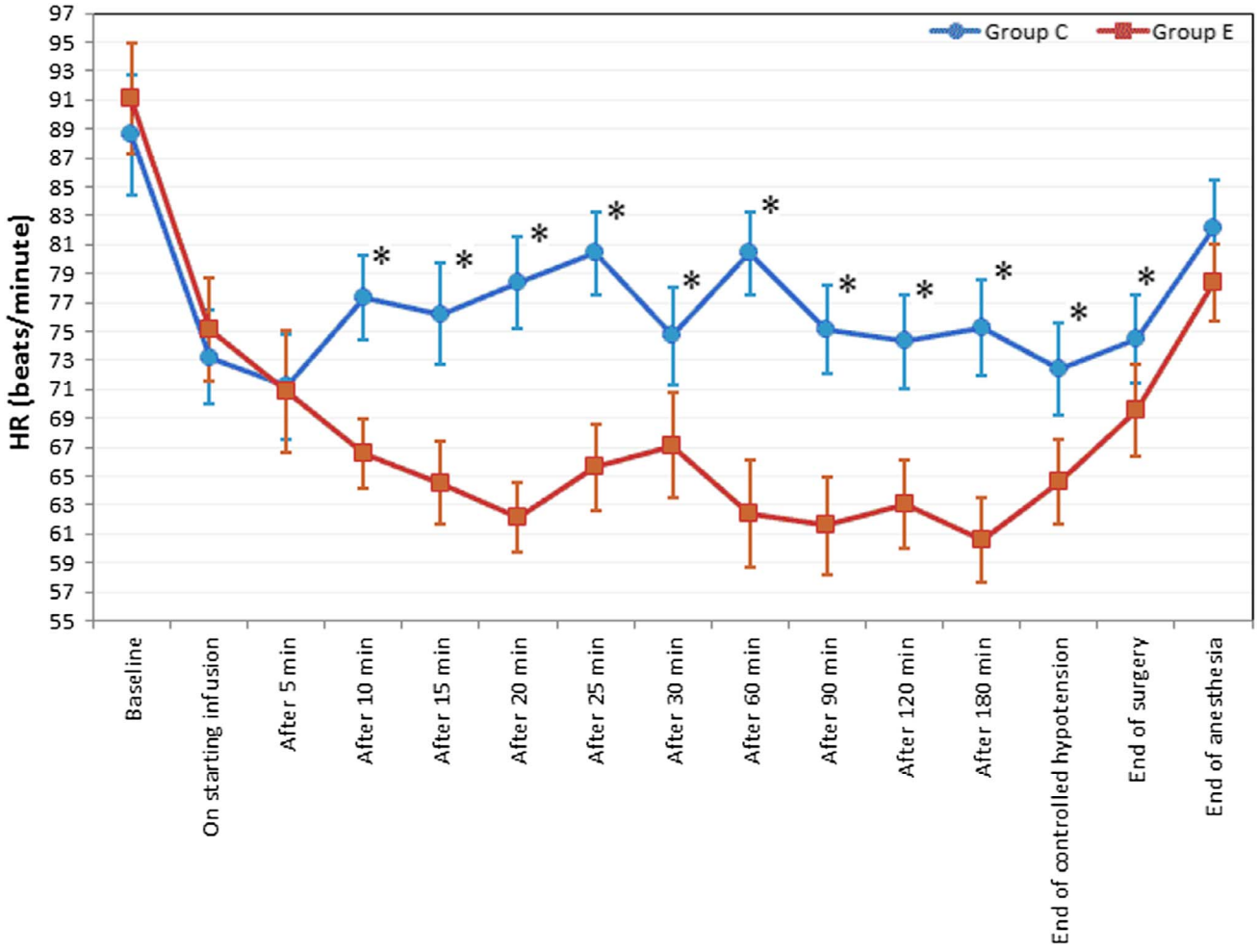

Fig. 3. Marker & error bar chart shows HR (beats/minute) at various times of measurements of the studied groups; markers represent mean; Y-error bar represent 95%confidence interval of mean, * indicate significant difference between the studied groups. HR = Heart rate.

nonsignificantly lower in clevidipine group the surgeon satisfaction score was significantly higher in clevidipine group compared to esmolol group. This can be attributed to the shorter time to reach target MAP with clevidipine and that more patients in esmolol group required nitroglycerine which causes peripheral venous vasodilatation that may lead to more oozing in the operative field.

There are some limitations of this study. Firstly, although clevidipine is prepared in a lipid emulsion and we used intralipid 10% as a placebo in esmolol group we didn't measure the lipid profile for the studied patients. But the total infused amount of the drug was small and the duration of infusion was relatively short. Secondly, it is a single center study and we recommend a future multicenter study including more number of patients.

5. Conclusion

Both clevidipine and esmolol are effective for inducing controlled hypotension during endoscopic repair of CSF rhinorrhea. Clevidipine has the advantage of shorter time to reach target MAP with less need of additional hypotensive agent and better surgeon satisfaction.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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