Comparative Study Between the Efficacy of Oral Verapamil and Oral Diltiazim on Reduction of Intraoperative Bleeding During Endoscopic Sinus Surgery Under General Anesthesia: A Randomized Controlled Trial


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Abstract

Background: Intra-operative bleeding presents a larger obstacle to endoscopic visualization. When profuse bleeding occurs, the blood pressure drops. This drop leads to a reduction or cessation of the bleeding, blood pressure stabilization, and recovery.

Objectives: Was to study the effect of addition of verapamil and diltiazim to general anesthesia aimed reduction in heart rate and blood loss during endoscopic sinus surgery, to study surgeon’s assessment of the surgical field and hemodynamic and to study effect of addition of verapamil and diltiazim to general anesthesia on serum cortisol and norepinephrine during endoscopic sinus surgery.

Patients and Methods: Quasi experimental research study conducted at Assiut University Hospital. A convenience sample of 135 male and female adult patients were classified into three equal groups included control group (45 patients) received placebo per oral (PO) 3 hours preoperative; diltiazim group (45 patients) received diltiazim 90mg (PO) 3 hours preoperative; and verapamil group (45 patients) received 80 mg PO 3 hours preoperative. The Primary outcome was to study the effect of addition of oral verapamil or diltiazim to general anesthesia on the Intraoperative hemodynamics: heart rate (HR), noninvasive blood pressure(NIBP), mean arterial blood pressure(MAP), and the blood loss during endoscopic sinus surgery and the Secondary outcome was To study the effect of addition of oral verapamil or Diltiazim to general anesthesia on the serum cortisol and norepinephrine during endoscopic sinus surgery and to study the surgeon assessment of surgical field.

Results: There was statistically significant difference between the three studied groups regarding the blood loss. The mean blood loss was 170.9± 19.0, 118.6± 17.3, and 100.5± 15.8 mL among the three studied groups. By post-hoc test there was statistically significant difference between group 1 and 2 (p<0.001), group 2 and 3 (p< 0.001) and group 1 and 3 (p<0.001). There were 11% in grade 1 among group 3. There was statistically significant difference between the three studied groups regarding the bleeding scale. There was statistically significant difference between the three studied groups regarding HR at different points of time intraoperative (5, 15, 30, 45, 60, 90, 120, 150 minutes). By post-hoc test there was statistically significant difference between group 1 and 2 (p<0.001), group 2 and 3 (p< 0.001) and group 1 and 3 (p<0.001). There was a statistically significant difference in the mean systolic blood pressure among the three studied groups at different points of
time intraoperative (5, 15, 30, 45, 60, 90, 120, 150 minutes). By post-hoc test there was statistically significant difference between group 1 and 2 (p <0.001), group 2 and 3 (p < 0.001) and group 1 and 3 (p<0.001), and there was a statistically significant difference in the mean diastolic blood pressure among the three studied groups at different points of time intraoperative (5, 15, 30, 45, 60, 90, 120, 150 minutes). By post-hoc test there was statistically significant difference between group 1 and 2 (p <0.001), group 2 and 3 (p < 0.001) and group 1 and 3 (p <0.001).

Conclusion: Both diltiazim and verapamil are effective and safe drugs for this purpose. The results revealed that better heart rate control in lesser time was achieved with verapamil. Thus, verapamil may be a better drug in cases where the goal is to achieve stricter rate control in less time. The results of this study support the use of verapamil for reduction of intraoperative bleeding than diltiazim when treatment with a calcium channel blocker is warranted. However, verapamil was better as it provided optimum surgical condition with only mild reduction in blood pressure. Reduced intra operative bleeding and less tachycardia throughout the surgery were added advantages.

Keywords: Diltiazim; Endoscopic Sinus Surgery Under General Anesthesia; Reduction Bleeding; Verapamil.

Introduction

Functional Endoscopic Sinus Surgery (FESS) is a minimally invasive technique used to restore sinus ventilation and function in patients with recurrent acute or chronic infective sinusitis in whom medical therapy has failed. The term FESS is used to draw attention to the potential for reestablishing natural mucociliary clearance mechanism, drainage and aeration of sinuses, and maintaining as much of the normal anatomy as possible. Over last few years this technique has become popular worldwide due to its minimally invasive nature and preservation of mucosa [1].

While great strides have been made in the domain of endoscopic imaging technology, visualization during FESS remains a challenge due to the vascularity of the narrow corridors of inflamed sinuses [2]. Intraoperative bleeding presents a larger obstacle to endoscopic visualization. Blood obscures the anatomy of the surgical field and dirties the endoscope lens leading to great difficulty in visualization. Continued bleeding into the surgical field during FESS not only impairs endoscopic vision, but also can lead to complications including: brain injury, orbital or optic nerve injury, and catastrophic bleeding from major vessels (e.g., internal carotid artery) [3].

A bloodless field in FESS is the ideal surgical state that rhinologists strive to achieve, and a significant amount of research and development has been dedicated to pursuing this aim in the last 10 years [3]. Various approaches have been used to secure a dry operating field, among them: conventional anesthesia, total intravenous anesthesia (TIVA) has been previously reported to result in reduced blood loss when used for FESS. However, few recent studies point out that (TIVA) may not significantly reduce blood loss. One way to achieve this goal “reduction of bleeding” is to induce controlled hypotension-controlled hypotension has been used to reduce bleeding and need for blood transfusions and provide a satisfactory bloodless surgical field [4].

New agents and techniques have been recently evaluated for their ability to induce effective hypotension without impairing the perfusion of vital organs [5].

Materials and Method

A randomized controlled study conducted in the trauma ICU at the Assiut University Hospital in Egypt was reviewed and approved by the Medical Ethics Committee in the Faculty of Medicine in Assiut University in Egypt (IRB no: 17101376) and performed in accordance with the ethical standards of the Declaration of Helsinki. Written informed consent was obtained from all patients or their legally authorized representatives prior to their inclusion in the study and after they had been informed of the benefits and risks of the investigation. We checked their electronic medical records to determine the eligibility criteria for the study. The study is registered in the ClinicalTrials.gov/ NCT04790331. This study adheres to the CONSORT guidelines.

Data were gathered between October 2020 and April 2021. Study the effect of addition of oral verapamil or diltiazim to general anesthesia on the intraoperative hemodynamics was considered the primary outcome, whereas the secondary outcome was the study the effect of addition of oral verapamil or diltiazim to general anesthesia on the serum cortisol and norepinephrine during endoscopic sinus surgery and to study the surgeon assessment of surgical field. The inclusion criteria were as follows: aged 18 years or older; hemodynamically stable. The exclusion criteria were as follows: any hypertensive patient on regular treatment rather than diltiazim or verapamil, any contraindication of calcium channel blocker as AV conduction defects (2nd and 3rd degree AV block), sick sinus syndrome, wolf-Parkinson-White Syndrome, history of congestive heart failure, patients on long-term β-blocker therapy and patients with allergy to medication included in the study.

Research Hypothesis

Better heart rate control in lesser time was achieved with verapamil with reduced intra operative bleeding and less tachycardia throughout the surgery.

Sample Size

Sample size calculation was carried out using G*Power 3 software (Faul et al., 2007) *. A calculated minimum sample of 135 patients will be needed. The sample will be divided into three groups control group (45 patients) received placebo per oral (PO) 3 hours preoperative; diltiazim group (45 patients) received diltiazim 90mg (PO) 3 hours preoperative; and verapamil group (45 patients) received 80 mg PO 3 hours preoperative will be needed to detect an effect size of 0.2 in the percentage of
bleeding loss level postoperatively, with an error probability of 0.05 and 80% power on a one-tailed test [6].

**Randomization**

Eligible patients were randomized into three equal groups, in which 45 patients were included for each group: control group; placebo group; and diltiazim group and verapamil group. Randomization occurred through data generated by the random.org online software. The researchers generated the sequence of numbers “blind” to the study after the selection of patients for eligibility criteria and disclosed prior to the start of the intervention program.

**Figure 1:** CONSORT flow diagram of a randomized controlled trial
**Intervention**

Baseline descriptive data collection occurred on the day of enrolment, which includes age, gender, pre-existing comorbidities, such as diabetes, coronary artery disease, asthma, peripheral vascular disease, renal failure, psychiatric disease, musculoskeletal disease, and others, obtained from the patient, patients’ family, and patients’ medical charts. Baseline laboratory data were recorded, including serum cortisol and norepinephrine test. Control group (45 patients) received placebo per oral (PO) 3 hours preoperative; diltiazim group (45 patients) received diltiazim 90mg (PO) 3 hours preoperative; and verapamil group (45 patients) received 80 mg PO 3 hours preoperative.

In the study, hourly monitoring of hemodynamics includes heart rate (HR), systolic blood pressure (SBP), MBP (Mean blood pressure), diastolic blood pressure (DBP), end tidal CO₂ (ET Co₂), arterial oxygen saturation (SaO₂) will be recorded every 5 minutes till the end of surgery, duration of surgery and estimated blood loss.

**Safety**

The patient was kept in the ICU for observation within 24 h following discontinuation of the study drugs to reduce the likelihood of hypotension or other side effects on discharge. If the blood pressure goal was met for more than 24 h without IV vasopressors, the study drug was discontinued prior to discharge to the ward. The accepting team was informed on the discharge that the patient had received a study drug. Instructions were given to the medical and nursing staff to contact a physician investigator if the patient became hypotensive in 24 h after the discharge in the ICU (defined as SBP <90 mmHg).

**Statistical Analysis**

All analyses were performed using the Statistical Package for the Social Sciences (SPSS) Statistical Software (IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY, USA). Continuous variables were presented as mean ± SD and categorical variables as frequencies. Differences between the groups at baseline were evaluated by an unpaired t test or the Mann–Whitney test for the comparison of continuous variables. The Chi-square test or Fisher’s exact test was employed to compare categorical variables. Analyses were performed by comparing baseline and post-intervention variables in the subgroups (control group versus midodrine group or minirin group).

**Results**

One hundred and thirty-five patients with spinal shock in the trauma ICU were evaluated according to the eligibility criteria for possible admission to the study, in which 135 patients were included. Figure 1 shows the flowchart of patient selection and composition of the groups.

**Preoperative Investigations**

There was no statistically significant difference between the three studied groups regarding cortisol. The mean cortisol was 8.3± 1.2, 8.4± 1.5, and 8.6± 1.4 among the three studied groups. There was no statistically significant difference between the three studied groups regarding noradrenaline. The mean noradrenaline was 457.2± 28.2, 446.9± 28.6, and 448.2± 30.2 among the three studied groups. There was no statistically significant difference between the three studied groups regarding Hb. The mean Hb was 11.5± 1.3, 12.2± 1.3, and 12.3± 1.5 among the three studied groups. There was no statistically significant difference between the three studied groups regarding platelet. The mean platelet was 209.1± 16.7, 206.4± 16.8, and 210.7± 14.8 among the three studied groups. There was no statistically significant difference between the three studied groups regarding PT. The mean PT was 11.4± 0.9, 11.6± 1.1, and 11.3± 1.1 among the three studied groups. (Figure 2, 3).

**Hemodynamics Monitoring**

As regard the baseline and during induction, the mean heart rate shows statistically significant difference among the three studied groups. While the mean heart rate was statistically significant difference among the three studied groups at different points of time intraoperative (5, 15, 30, 45, 60, 90, 120, 150 minutes). By post-hoc test there was statistically significant difference between group 1 and 2 (p<0.001), group 2 and 3 (p< 0.001) and group 1 and 3 (p<0.001) (Figure 4).
As regard the baseline and during induction, the mean systolic blood pressure shows insignificant differences among the three studied groups. While the mean systolic blood pressure was statistically significant difference among the three studied groups at different points of time intraoperative (5, 15, 30, 45, 60, 90, 120, 150 minutes). By post-hoc test there was statistically significant difference between group 1 and 2 (p<0.001), group 2 and 3 (p<0.001) and group 1 and 3 (p<0.001) (Figure 5).

**Blood loss**

The mean blood loss was 170.9± 19.0, 118.6± 17.3, and 100.5± 15.8 mL among the three studied groups. There was statistically significant difference between the three studied groups regarding blood loss. By post-hoc test there was statistically significant difference between group 1 and 2 (p<0.001), group 2 and 3 (p<0.001) and group 1 and 3 (p<0.001). There were 11% in grade 1 among group 3. There was statistically significant difference between the three studied groups regarding the bleeding scale (Figure 6).

**Discussion**

The outcome of endoscopic sinus surgery (FESS) depends on many factors, one of the most important being a clean surgical field during the procedure. Excessive bleeding can severely compromise the already restricted endoscopic view and thus lead to increased incidence of both major and minor complications. Different techniques have been described in the attempt to minimize bleeding and enhance visibility during FESS. [7].

This Quasi-experimental research conducted among 135 consecutive patients and aimed to study the effect of addition of oral verapamil or diltiazem to general anesthesia on the intraoperative hemodynamics: heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial blood pressure (MAP), arterial oxygen saturation (Sao2), duration of the surgery and the blood loss during FESS. To our knowledge this is the first study that discussed such issue. In our study, results found that regarding the mean systolic and diastolic blood pressure, regarding the baseline and during intubation, they showed insignificant differences among the three studied groups while there was statistically significant difference among the three groups at different points of time intraoperative.

The systolic and diastolic blood pressure was significantly reduced by verapamil more than diltiazim. Both were significantly lower than the control group. There was statistically significant differences among the three studied groups 5 minutes after intubation.
duction, intraoperative (5, 15, 30, 45, 60, 90, 120, 150 minutes) and postoperative. A systematic review and meta-analysis conducted by Lin and Ma, (2018) to assess the efficacy and safety of CCB in treating perioperative hypertension compared with other antihypertensive agents. They found that CCB can significantly decreased perioperative blood pressure [8].

In agreement with this Phillips (1997) found that at baseline, mean systolic blood pressures were 139± 15 and 136 ±17 mm Hg for the diltiazim and verapamil groups, respectively with no significant 94 difference. Mean diastolic blood pressures at baseline were 85±18 in patients receiving diltiazim and 77± 20 mm Hg in the verapamil group with no significant difference [9].

In our study results, there was statistically significant differences between control and diltiazim (P>0.001), diltiazim and verapamil (P>0.001), and control and verapamil (P>0.001) regarding the heart rate. The heart rate was significantly lower by verapamil than diltiazam; both were significantly lower than control group. The mean heart rate was statistically significant differ among the three studied groups at baseline, during induction, and post-operative (5, 15, 30, 45, 60, 90, 120, 150 minutes) and post-operative. In agreement with our results, a recent study by Agawam, (2020) was conducted to compared the safety and efficacy of these drugs for the management of Atrial fibrillation. They demonstrated that heart rate was statistically significant different between verapamil and diltiazam (p = 0.002) as the heart rate was significantly lower among verapamil group [10].

In a case report published by Wang et al., (2019) about female 92 years old with baseline heart rate was measured at 155 beats/ min with completely uneven rhythm. After diltiazim was administered the patient's heart rate did not improve under the control and her blood pressure significantly decreased. Then they replaced diltiazim with 40 mg verapamil 3 times a day, and the patient converted to sinus rhythm with a heart rate of 70 beats/ min after 9 days of application [11].

In a retrospective study by Rajput, (2020) revealed that heart rate was significantly decreased in verapamil and diltiazam groups (p < 0.001) with treatment. The verapamil had lower heart rate than diltiazam group after 30 minutes from induction with no statistically significant difference [12]. A study by Pham, (2020) aimed to evaluate whether addition of verapamil into local anesthetic for brachial plexus block provide additional anesthetic and analgesic effects. Mean oxygen saturation in Group A without verapamil and Group B with verapamil ranged from 98 ± 0.5% to 99 ± 0.57% and 98 ± 0.5% to 99 ± 0.49% respectively. The oxygen saturation was not statistically different at any point during the entire follow up period [13].

Our study results found that regarding the blood loss, there was statistically significant difference between the three studied groups. The mean blood loss was (170.9± 19.0 control group), 118.6± 17.3(diltiazam group), and 100.5± 15.8 mL (verapamil group). By post-hoc test there was statistically significant difference between group 1 and 2 (p<0.001), group 2 and 3 (p<0.001) and group 1 and 3 (p<0.001). There was less blood loss in verapamil group than the diltiazam group than control group. In our opinion, this could probably be due to lower intraoperative heart rate which has been shown previously to reduce the amount of blood loss.

The surgical duration has been shown to be shorter when controlled hypotension technique is used probably because of better visibility of surgical field and less time spent in repeated suctioning [14]. A study by Manikandan, (2019) conducted to find out the need of rescue analgesia in first 24 hours and number of rescue analgesia required in first 24 hours. They found that the mean time for duration of surgery was comparable in group with or without verapamil, for Group without verapamil mean duration were 102.9±9.95 minutes and for Group 2 with verapamil mean duration were 98.3±11.38 minutes. P value of 0.1031 which is insignificant [15].

**Conclusions**

This Quasi-experimental research study revealed that better heart rate control in lesser time was achieved with verapamil. Thus, verapamil may be a better drug in cases where the goal is to achieve stricter rate control in less time. The results of this study support the use of verapamil for reduction of intraoperative bleeding than diltiazem when treatment with a calcium channel blocker is warranted.

**Data Availability**

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

**Conflicts of Interest**

The authors declare that there are no conflicts of interest regarding the publication of this paper.

**Funding Statement**

This research did not receive any specific grants from funding agencies in the public, commercial, or not-for-profit sectors.

**Acknowledgments**

The authors thank all patients who participated in the study. The authors express their gratitude to critical care physicians and nurses caring for patients in the ICUs where the study was done.

**References**


