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Original Article

THE EFFECTS OF SUBMUCOSAL EPİNEPHRINE INJECTION IN ENDOSCOPIC PROCEDURES ON CARDIOVASCULAR SYSTEM

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ABSTRACT:

Objectives: The purpose of this study is to investigate the cardiac safety of epinephrine injections into the gastrointestinal tract submucosa.

Methods: The patients who underwent endoscopy and had epinephrine injected for bleeding control, as well as a control group who underwent endoscopy but did not receive epinephrine, were included in the study. Systolic and diastolic blood pressure (mmHg) and heart rate (beats) were measured at 0, 3, 6, 9, and 12 minutes after epinephrine injection in 1/1000, 1/10,000, and 1/20,000 concentrations of patients, and similarly, without administration of epinephrine in the control group.

Results: The change in systolic and diastolic blood pressure values over time was not significant in the groups that received the epinephrine dose (p=0.059, p=0.117). Similarly, no significant difference was found between groups with different epinephrine concentrations in the same minute (p=0.889). There was no significant difference in heart rate values between all groups (p=0.390).

Conclusion: In this study, epinephrine was found to be cardiovascularly safe in cases where it was necessary to exceed the daily dose used in extraesophageal procedures.

KeyWords: Epinephrine, Cardiovascular System, Endoscopy, Hypertension

INTRODUCTION:

Endoscopic epinephrine submucosal injection is effective and easy to use in providing hemostasis; It is a sympathomimetic agent that is frequently used during many endoscopic procedures, especially in gastrointestinal tract bleeding, polypectomies, endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) (1,2). Sympathomimetic agents cause an increase in heart rate, increase in myocardial contraction force, and relaxation of bronchial muscles due to their general effects. In contrast, they cause vasoconstriction in some parts of the body and vasodilation in some parts of the body. Theseeffectsareprovidedthrough α and β adrenergicreceptors (3).

Previouspharmacodynamicandpharmacokineticstudiesshowthatorallyadministeredepinephrine is degraded by gastric or small intestine enzymes, whereas epinephrine given to the portal vein is

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degraded in the liver and supports the absence of systemic effects of epinephrine. Andthestudyshowedthat, only when high doses of epinephrine were given orally did it affect the blood pressure of experimental animals (4).

Side effects that can be seen especially from the cardiac point of view may necessitate limiting the use of epinephrine in specific patient groups, as it may have serious effects in patients with coronary disease, patients with uncontrolled thyrotoxicosis, and patients using monoamine oxidase (MAO) inhibitors or tricyclic antidepressants (3). However, the number of studies investigating this issue is very few.

This study aims to investigate the cardiac safety of epinephrine injection into the gastrointestinal tract submucosa, which has been routinely administered for years in clinical practice.

Materials and Methods:

Study Group

The present study was conducted in a tertiary hospital between August 2019 and February 2020. The study is a single-center and prospective study in which patients who underwent endoscopy and epinephrine performed for bleeding control because of polypectomy, and endoscopic retrograde cholangiopancreatography (ERCP), and a control group who underwent endoscopy for dyspeptic reasons but did not receive epinephrine were included.

Patients under 18 years of age, with severe cardiovascular or pulmonary disease, with a history of endocrine (thyrotoxicosis, parathyroid disease) disease that may affect the study, pregnant or lactating female patients, and patients who did not give informed consent were excluded from the study.

Endoscopic Procedures:

The patients were selected from those who volunteered to participate in the study, and a written informed consent form was obtained. Endoscopic procedures were performed by a single gastroenterologist with 10 years of endoscopy experience, and a video endoscopy system was used in all procedures (Olympus Corporation; Tokyo, Japan). Topical lidocaine was sprayed on all patients before the procedure, and sedo-analgesia was administered with intravenous 2 mg midazolam and 25 mcg of fentanyl. Ethical approval was obtained from the local ethics committee.

Clinical Evaluation and Sample Collection:

Systolicanddiastolicbloodpressure (mmHg) and heart rate (beats) at 0, 3, 6, 9, and 12 minutes after epinephrine injection in 1/1000, 1/10,000, 1/20,000 concentrations of the patient group were measured, and likewise, without administration of epinephrine in the control group values were measured. Afterward, the cardiac safety and side effects of submucosal epinephrine injection were evaluated. SeaMed Superview-12 bedside monitor was used for blood pressure and heart rate measurements of the patients.

It was carried out by the principles of the Declaration of Helsinki, with the permission of Duzce University Ethics Committee dated 05.08.2019 and decision number 2019/162.

Statistical analysis:

The "Multiple Chi-Square Test" was used in the statistical evaluation of demographic data. Inthestatisticalevaluation of the comparison parameters, the"RepeatedMeasures ANOVA" method was applied to investigate the effects of epinephrine injection given at different concentrations over time on our parameters. Statistical analyzes were performed with the SPSS v.22 package program, the significance level was

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considered 0.05, and p≤0.05 was considered statistically significant.

Results:

A total of 146 patients were included in the study, 38 patients who received epinephrine at a titer of 1/1000, 34 patients at a titer of 1/10.000, 39 patients at a titer of 1/20.000, and 35 patients in the control group without epinephrine. 26% (n=38) of thecaseswerefromthegroup of patientswhoreceivedepinephrine at a titer of 1/1000, 23% (n=34) fromthegroupadministered 1/10,000, 27% (n=39) fromthegroupadministered 1/20,000, and% 24 (n=35) consisted of thecontrolgroupwhounderwentendoscopyfordyspept icreasonsanddid not receiveepinephrine. 58% (n=85) of our total cases consisted of female cases and 42% (n=61) male cases, the mean age of all groups was 60.2±18.9 (18-92) (Table 1)

58% (n=85) of the patients included in the study had a comorbid disease, and 42% (n=61) had no history of chronic disease. 19% (n=28) of our cases were using beta blockers. In our study, the rate of patients using any anti-hypertensive agent other than beta-blockers was 33% (n=48) (Table 1).

Patients were examined for changes in systolic and diastolic blood pressure as a result of the injection of different epinephrine concentrations (Table 2). When the changes in the groups for systolic blood pressure were analyzed over time, it was found that the interaction of the groups injected at different titers with time was not significant (p=0.786). However, no significant difference was found between the groups with different epinephrine concentrations in the same minute (p=0.395). Similarly, the change in systolic blood pressure values over time was not significant within the groups that received the same titer of epinephrine (p=0.059) (Figure 1).

When the changes in the groups in terms of diastolic blood pressure were examined over time, it was found that the interaction of the groups injected at different titers with time was not significant (p=0.117). Likewise, there was no significant difference between the groups with different epinephrine concentrations in the same minute (p=0.889). However, time was found to have a significant effect on diastolic blood pressure within the groups receiving the same titer of epinephrine (p=0.002). That is diastolic blood pressure was found to increase significantly over time in all study groups, regardless of epinephrine injection (Figure 2).

When the heart rate values of the patients were compared, it was found that the interaction of the groups injected with different titers with time was not significant (p=0.390). In addition, there was no significant difference between the groups with different epinephrine titers in the same minute (p=0.073). However, time was found to have a significant effect on heart rate within the groups that received the same titer of epinephrine (p=0.01). That is heart rate was found to increase significantly over time in all study groups, regardless of epinephrine injection (Figure 3).

Discussion:

In this study, epinephrine was found to be cardiovascularly safe in cases where it is necessary to exceed the dose applied in daily practice in extraesophageal procedures.

It is thought that epinephrine causes vasoconstriction in the applied area and probably has a direct effect on the coagulation processes in the arterial defect area (5). For this reason, epinephrine has become a popular agent in the majority of cases in endoscopic techniques for bleeding control, for the prophylaxis of bleeding after polypectomy, submucosal lift before PMR and ESD, or after the endoscopic procedure (6).

When studies are examined, a few cases of tissue necrosis, intramural hematoma, and gastric perforation have been reported associated with endoscopic epinephrine injection (7-9). However,

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there are not enough studies examining the potential hemodynamic effects of epinephrine, which is known to have serious cardiac complications in systemic circulation, following submucosal injection.

In a studybySarmentoJunior KM et al., various concentrations of topical epinephrine were administered to patients during nasal endoscopic surgery and its systemic effects were investigated. Patients in the groups treated with topical epinephrine at titers of 1:2000 and 1:10000 showed a significant increase in blood pressure when compared with the other group (those applied at a titer of 1:50,000), but no significant difference was observed in terms of heart rate (10).

In our study, submucosal epinephrine was applied to the gastrointestinal tract, and no significant difference was found between the groups in terms of blood pressure and pulse parameters.

In another study, the systemic effects of submucosal local anesthetic and epinephrine combination during endoscopic nasal sinus surgery were investigated and it was reported that significant increases in systolic, diastolic blood pressure and heart rate were recorded after submucosal injection of 1:100,000 epinephrine and 2% lidocaine. On the other hand, it was reported that the same effect was not observed in patients treated with a mixture of 1:200.000 epinephrine and 2% lidocaine (11). Thiseffect, which was not observed in our study on the gastrointestinal tract, was thought to be due to the high vascularity of the nasal anatomy and the direct delivery of epinephrine to the systemic circulation via the superior vena cava without being metabolized in the liver.

Inanotherstudyinvestigatingthesystemicabsorption of epinephrine after endoscopic submucosal injection, plasma catecholamine levels of patients were measured at certain times after injection, and upto 4-5-fold increases were observed in plasma levels immediately after injection, and it was observed that they returned to their basal levels within 20 minutes. In this study, although blood pressure and pulse values were not recorded, it was recommended to be careful in terms of cardiac care, especially after the first injection (12). Considering the 146 patients in our study, no significant difference was observed in terms of the parameters we followed, indicating the systemic absorption of epinephrine, and no cardiovascular complications were observed. The fact that we have shown that there is no increase in blood pressure and pulse values despite the increase in plasma rate of epinephrine by 4-5 times is an important finding in that it can be used safely, especially in patients with heart failure and arrhythmia potential. We think that this is related to the fact that epinephrine is eliminated after mixing with the plasma before it has a cardiovascular effect. It may also be associated with a decrease in the efficacy of epinephrine as it is metabolized in the liver.

In a study by C. Schlag et al., animals were subjected to endoscopy under general anesthesia, and animals were divided into three groups and were administered 5 milliliters of saline (0.9% NaCl), 2.5 milliliters and 5 milliliters of epinephrine (at a titer of 1:10,000) during the procedure. The study was divided into sections as the esophagus, stomach corpus, and antrum, and it was shown that there were significant increases in heart rate, especially in injections into the esophagus (13).

In our study, no significant difference was found between the groups in terms of blood pressure and heart rate at different titers and doses. The injections were made into the stomach and duodenum and no application was made to the esophagus. This difference between studies can be explained by different venous drainage pathways of the esophagus and stomach. The drainage of the 2/3 proximal part of the esophagus passes the portal system and hepatic metabolism, and directly into the systemic circulation via the superior vena cava, and the drainage of the distal 1/3 into the portal vein via the left gastric vein. On the other hand, catechol-o-methyltransferase and monoamine oxidase enzymes in the liver cause significant first-

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pass elimination of catecholamines through drainage through the portal system (14,15).

InAotherstudyconducted in the United Kingdom, it was reported that a series of transient cardiac arrhythmias and hypertensive attacks were observed following epinephrine injection during the endoscopic procedure (16). However, no detailed information on cardiac adverse events or evidence of cardiac ischemia has been reported.

ItwasrecentlyshownbyPeleman et al. that the use of intranasal topical 1:1000 epinephrine during endoscopic sinus surgery (ESS) did not cause significant hemodynamic changes or electrocardiographic abnormalities in patients before and after ESS (17). In our study, we observed that there was no arrhythmia in the monitor follow-up during the procedure. Similarly, we think that submucosal epinephrine administration does not cause arrhythmia.

In our study, which was conducted to better observe the systemic effects of epinephrine from different perspectives, there are some limitations in this regard, since esophageal injection was not used. Other limitations of our study; were carried out in a single center.

We believe that our study will shed light on randomized controlled studies with a higher number of patients on this subject.

Conclusion:

In this study, it has been shown that the use of epinephrine, especially in extra esophageal endoscopic procedures, is safe in terms of its effects on thecardiovascular system. Epinephrine injection can be safely performed to patients with dysrhythmias, hypertension and coronary artery disease.

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