# Comparison of the Effects of Levobupivacaine with Lidocaine-Epinephrine on Decongestion and Bleeding during Functional Endoscopic Sinus Surgery

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**Abstract:** *Background and Objectives*: Bleeding and congestion during functional endoscopic sinus surgery (FESS) can affect directly to the visibility of safe landmarks and surgical outcomes. Levobupivacaine is a long-acting local anesthetic with inherent local vasoconstrictor activity that is effective when administered by local infiltration to the skin. We aimed to compare the use of pre-incision levobupivacaine and lidocaine 2% with epinephrine for intraoperative vasoconstriction and postoperative analgesia in patients undergoing functional endoscopic sinus surgery.

*Methods*: After institutional approval and informed patient consent, fifty six patients were randomly assigned to receive preincisional local infiltration under general anesthesia. Group LB received levobupivacaine 0.25% (n=28) and group LD-E (n=28) received epinephrine plus lidocaine 2%. Decongestion level of the middle turbinate, the occurrence of hemodynamic variability, intraoperative bleeding scores, the quality of the surgical field, and the first rescue analgesic time in 24 h of all patients were recorded. At the 10$^{th}$ minute, nasal mucosa images were more decongested compared to the images at 5$^{th}$ minute in levobupivacaine and lidocaine plus epinephrine groups (p=0.00 and p=0.01 respectively).

*Results*: Decongestion level of the middle turbinate, intraoperative bleeding scores, the quality of the surgical field and first rescue analgesic time were similar between the groups (p>0.05).

*Conclusions*: Levobupivacaine may be an alternative to lidocaine plus epinephrine because it provides similar surgical visibility and postoperative analgesia in patients undergoing FESS.

**Keywords:** Functional endoscopic sinus surgery, levobupivacaine, lidocaine, bleeding.

## INTRODUCTION

Functional endoscopic sinus surgery (FESS) is a commonly performed procedure in the head and neck field. It is known that bleeding during FESS can affect directly to the visibility of safe landmarks and surgical outcomes [1]. Local injection of epinephrine containing local anesthetics is widely used in order to enhance hemostasis, decrease surgical bleeding, allow to better visualizing surgical landmarks during surgery by reducing mucosal blood flow and also relieve pain [2,3]. Use of vasoactive drugs to control bleeding is not without pitfalls. Systemic effects of epinephrine may constitute a potential hazard in patients with hypertension, ischemic heart disease, anemia, preexistent liver or renal damage and endocrine dysfunction (hyperthyroidism, pheochromocytoma and diabetes mellitus) [4,5]. It would be more desirable to identify and use anesthetics with inherent local vasoconstrictor activity to refrain from the unwanted systematic effects of epinephrine.

Levobupivacaine is a long-acting amide local anesthetic with vasoconstrictive activity that is effective when administered by local infiltration to the skin [6,7]. Demiraran *et al.* [4] have shown that local submucosal infiltration of levobupivacaine is as effective as lidocaine plus epinephrine combination in nasal surgeries for the control of bleeding. Their conclusion was indirectly based on similar perioperative and postoperative hemoglobin and hematocrit values. There is no study which compares the effectiveness of levobupivacaine and lidocaine plus epinephrine on the visual quality of the surgical field during FESS. The primary aim of this prospective, randomized, double blind study was to compare the visual quality of the surgical field, decongestion level of the middle turbinate, and the secondary aim was to compare the postoperative pain of the patients after local infiltration with levobupivacaine and lidocaine plus epinephrine at clinically relevant concentrations in patients undergoing FESS under general anesthesia.

## METHODS

After obtaining informed consent, we enrolled 56 non-smoking patients undergoing FESS with or without septoplasty under general anesthesia into the study. All patients were categorized as grade I or grade II according to the American Society of Anesthesiologists criteria and class I or class II according to Lund-

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Mackay classification system [8]. Patients who had any mental disturbance, neurological disease, or allergy to local anesthetics, a history of alcohol or drug abuse and patients undergoing tumor resection, nasal polyposis, or allergic fungal sinusitis were excluded from the study.

Patients were randomly allocated into one of two groups according to computer generated random numbers to receive either 0.25% levobupivacaine (Chirocaine® 0.25 % Abbott, Norway) (Group LB; n = 28) or lidocaine 2% with 1:200 000 epinephrine (Jetocaine®, Adeka, Turkey) (Group LD-E; n = 28) as a pre-incision local infiltration to the middle turbinate, uncinate process and sphenopallatine ganglion. The study drugs were prepared by a team member who took no further part in the study. The surgeon, the anesthesiologist and the patients were blinded as to group assignment until the end of the study.

All patients were put in a 15 degree head-up supine position. An oxymetazoline hydrochloride (0.5 mg $mL^{-1}$) solution spray was puffed into each nostril before starting anesthesia. After routine monitoring, heart rate (HR) and non invasive arterial blood pressures were recorded before induction of anesthesia and then every 5 min until discharge from the theatre. Anesthesia was induced with 2 μg $kg^{-1}$ fentanyl, 3 mg $kg^{-1}$ propofol, and 0.6 mg $kg^{-1}$ rocuronium, and maintained with continuous infusion of remifentanil (0.1–2 μg $kg^{-1}min^{-1}$), 50% nitrous oxide in oxygen and desflurane. Ventilatory rate was adjusted to maintain end tidal CO2 of 34-40 mmHg. Systolic blood pressures of the patients were maintained at 100 ± 10 mmHg by adjusting the level of anesthesia with desflurane and infusion of remifentanil before the local anesthetic injection of the middle turbinates. Patients whom systolic blood pressures were lower than 90 mmHg or higher than 110 mmHg despite anesthetic intervention were excluded from the study. The same surgeon performed all procedures. Before the injection of the study drug, video of endoscopic examination by a zero degree telescope of the middle turbinate and nasal cavity was recorded using a high resolution recording system. Patients who underwent FESS received 3 mL of the study solution to both middle turbinates, uncinate processes and sphenopallatine ganglion (total of 6 mL) and patients who underwent septoplasty received an additional 6 mL of the study solution to nasal septum. Endoscopic image recordings were repeated at 5 and 10 minutes after the local anesthetic injection. Arterial pressures and heart rate were recorded at baseline and 60-second-intervals for 10 minutes after the infiltration. The episode of adverse reactions during the first 10 minute, including hypotension (decrease in systolic arterial blood pressure from 20% of baseline), hypertension (increase in systolic arterial blood pressure from 20% of baseline), bradycardia (decrease in heart rate from 20% of baseline) and tachycardia (increase in heart rate from 20% of baseline) were recorded. Intraoperative bleeding was evaluated using a 100 mm visual analog scale (VAS); 0 = no bleeding and 100 = the worst possible bleeding, by the surgeon at the end of the FESS. The quality of the surgical field was evaluated by the surgeon and scored as, excellent (no mucosal bleeding), good (mild mucosal bleeding or discomfort, no need for packing), moderate (moderate mucosal bleeding that required packing and waiting), or poor (severe mucosal bleeding that interfered with surgery) at the end of the FESS procedure. The recorded injection image files were scored by three blinded ENT surgeons for the decongestion level of the middle turbinates using three- point scale (0: decongested, 1: unchanged, 2: congested) by comparing them with their pre-injection images.

Patients were instructed on how to use the VAS scale for the assessment and localization (nasal region or the others) of pain prior to surgery. Pain was scored at 30 min, 1 h, 3 h, 6 h, 12 h and 24 h after surgery by the patients. Rescue analgesics (acetaminophen 1gr intravenously) were given at the request of the patients or if the VAS was higher than 30. Number of patients receiving analgesic, time to the first rescue analgesic and totally analgesic consumption were recorded.

A power calculation ensured that 48 patients (24 patients for each group) were recruited to provide 90% power for a difference in VAS from 20 mm versus 30 mm at the 5% significance level. Because we planned to exclude patients with variations in systolic blood pressure prior to local anesthetic infiltration we increased the total number of patients to 56.

Data was presented as mean ± standard deviation. Mann-Whitney U to compare between two non-parametric independent variables, and Wilcoxon Signed Ranks test to compare between two non-parametric dependent variables. Categorical variables were analyzed using chi- square test to determine the differences among the groups. The Fischer's exact test was used as appropriate. The level of significance was set at $p< 0.05$.

## RESULTS

Four patients were excluded due to variations in systolic blood pressure prior to local anesthetic infiltration. Fifty two patients completed the study (28 in group LB and 24 in group LD-E). Nine patients (6 in group LB and 3 in group LD-E) were excluded from the pain assessment because of rescue analgesic use for treatment of postoperative sore throat.

There were no differences between groups regarding age, gender, duration of surgery, and operation types (Table **1**). Bleeding scores and the quality of the surgical field were similar between the groups (Table **2**). Decongestion scores were similar between the groups (Table **3**). At the 10$^{th}$ minute, nasal mucosa images were more decongested compared to the images at 5$^{th}$ minute in levobupivacaine and lidocaine plus ephinephrine groups (p=0.00 and p=0.01 respectively) (Table **3**). At the 30$^{th}$ min and 1 h, 3 h, 6 h, 12 h and 24 h, VAS values, number of patients who need rescue analgesic, first rescue analgesic time and analgesic consumption during the first 24 h were similar between the groups (Table **4**). No episode of hypotension, hypertension, tachycardia or bradycardia was recorded during the first ten minutes after local anesthetic injection.

**Table 1. Demographic Data**

| | Grup LB (n=28) | Grup LD-E (n=24) |
|---|---|---|
| **Age** | 35.2 ± 13 | 34.9 ± 15 |
| **Gender** (m/f) | 17/11 | 17/7 |
| **Duration of surgery** (min) | 75.7 ± 23 | 68.5 ± 20 |
| **Procedures** | | |
| FESS / FESS with septoplasty | 16 / 11 | 11 / 13 |

Data are presented as mean ±standard deviation. **FESS**: Functional endoscopic sinus surgery, **LB**: Levobupivacaine, **LD-E**: Lidocaine plus epinephrine, p>0.05

**Table 2: Intraoperative Bleeding Scores and Quality of the Surgical Field**

| | Group LB (n=28) | Group LD-E (n=24) |
|---|---|---|
| **Bleeding Scores (*)** | 29.4±16 | 29.5±18 |
| **Quality of the surgical field** | | |
| Excellent / good / moderate / poor | 2 / 4 / 18 / 4 | 3 / 2 / 14 / 5 |

Data are presented as mean ±standard deviation. **LB**: Levobupivacaine, **LD-E**: Lidocaine plus epinephrine, *: Evaluated using a 100 mm Visual Analog Scale 0 = no bleeding and 100 = the worst possible bleeding, p>0.05

**Table 3: Decongestion Level of the Middle Turbinate**

| | Group LB (n=28) | Group LD-E (n=24) | p |
|---|---|---|---|
| **5$^{th}$ min** 0 / 1 / 2 | 9 / 13 / 6 (32) / (46) / (21) | 6 / 9 / 9 (25) / (37) / (37) | >0.05 |
| **10$^{th}$ min** 0 / 1 / 2 | 23 / 4 / 1* (82) / (14) / (4) | 18 / 4 / 2 # (75) / (16) / (8) | >0.05 |

Data are presented as n (%). LB: Levobupivacaine, LD-E: Lidocaine plus epinephrine. **0**: decongested, **1**: unchanged, **2**: congested, * p=0.00 when compared with 5$^{th}$ min of Group LB, # p=0.01 when compared with 5$^{th}$ min of Group LD-E.

**Table 4: Postoperative Pain Scores and Rescue Analgesic Consumption**

| | Group LB (n=22) | Group LD-E (n=21) |
|---|---|---|
| **VAS values** | | |
| 30 min | 23.6 ± 6 | 20.9 ± 4 |
| 1 h | 26.3 ± 7 | 22.3 ± 8 |
| 3 h | 25.9 ± 6 | 30.4 ± 13 |
| 6 h | 22.7 ± 5 | 24.2 ± 6 |
| 12 h | 20.9 ± 4 | 21.4 ± 5 |
| 24 h | 18.6 ± 6 | 19.0 ± 6 |
| Number of patients receiving analgesics | 15 | 14 |
| Time to the first rescue analgesic (min) | 668.4 ± 545 | 672.6 ± 510 |
| Analgesic consumption (mg) | 535.7 ± 507 | 625.0 ± 494 |

Data are presented as mean ±standard deviation. **LB**: Levobupivacaine, **LD-E**: Lidocaine plus epinephrine, **VAS**: Visual analog scale, p>0.05, **p.s.:** Six in group LB and 3 in group LD-E were excluded from the pain assessment because of rescue analgesic use for treatment of postoperative sore throat.

## DISCUSSION

This study demonstrates that local injection of levobupivacaine has a similar effect as lidocaine plus ephinephrine on the decongestion of middle turbinate, bleeding scores, visual quality of surgical field during the surgery and reduction of postoperative pain in patients undergoing FESS.

It is mandatory for the surgeon to maintain a clean endoscopic view during FESS. Local vasoconstriction can be used to reduce blood flow to the nasal sinus tissue. Local anesthetics combined with ephinephrine are commonly infiltrated into the sinuses to guarantee better visibility and postoperative analgesia [9]. A small amount of these solutions is absorbed systemically and serious adverse consequences have been reported such as arrhythmias, uncontrolled hypertension, myocardial infarction, stroke and cardiogenic shock [9].

There is a significant debate in the literature including the benefits and risks and also effectiveness of using epinephrine in order to reduce mucosal blood flow [2,3,5,9-12]. Javer *et al.* [10] reported that there is no significant reduction in intraoperative blood loss during FESS when local anesthetic containing epinephrine is used compared with infiltration with normal saline. Unfortunately our study does not add new information to this debate. We conducted a pilot study consisting of ten patients before designing the present study which revealed that patients in the saline group had higher bleeding scores than in the lidocaine plus epinephrine group (VAS >30 all five patients and VAS >30 one of five patients respectively). As normal saline results in high bleeding scores, considering ethical issues we did not to include a placebo arm in our study.

In the present study, serious epinephrine related cardiovascular side effects including hypertension, hypotension, tachycardia, bradycardia, arrhythmias and cardiac arrest were not observed. Submucosal injection of lidocaine 2%, with 1:200000 epinephrine during FESS does not lead to hemodynamic fluctuations or increased intraoperative bleeding compared with lidocaine, 2%, with 1:100000 epinephrine [12]. On the other hand Javer *et al.* [10] reported that a significantly higher arterial blood pressure associated with infiltration of bupivacaine with 1:200000 epinephrine in patient undergoing FESS. Stable hemodynamics may be explained with the relatively young and healthy profile of our patient population and/or 1:200000 concentration of epinephrine and protective effects of lidocaine [13]. Our study design did not include invasive arterial pressure monitoring. Recording non invasive blood pressure and heart rate one minute apart may have missed any fluctuation due to epinephrine which is known to increase at 1.5 minutes after the beginning of local infiltration [14].

Previous work has shown that levobupivacaine, the S (-) isomer of bupivacaine, exhibits vasoconstrictive properties when administered intradermally [6,7]. This observation was later questioned by Newton *et al.* [7] who showed that levobupivacaine has a biphasic effect on skin micro vessels with vasodilatation proceeded with vasoconstriction after $40^{th}$ minutes. The vasoconstriction Newton *et al.* [7] observed with ≤ 0.125% levobupivacaine concentration. In the present study, decongestion was evaluated 5 and 10 minutes after local anesthetic infiltration and bleeding was evaluated 10 minutes after local anesthetic infiltration. Nasal mucosa images were more decongested at the $10^{th}$ minute compared to $5^{th}$ minute images both with levobupivacaine and lidocaine plus epinephrine. Our results are not consistent with a biphasic response of the nasal mucosa with more apparent decongestion in the later phase. This may be explained by the possible different vasoreactivity profile of different vessels to local anesthetics. Newton *et al.* [7] have hypothesized that the vasoconstriction caused by lower doses of levobupivacaine may be result of the gradually washing away of the drug injected in to the skin. Presumably the levobupivacaine we administered in to the nasal mucosa which is richer in capillary blood flow was washed away more rapidly than the skin. Local levobupivacaine concentration may have reduced to the low vasoconstrictor threshold level within 10 minutes in nasal mucosa compared to 40 minutes in skin in Newton et al study. Further studies are needed for the effects of low dose levobupivacaine in patients undergoing FESS.

There is limited information on the effectiveness of levobupivacaine for decreasing surgical bleeding in patients undergoing nasal surgery. Demiraran *et al.* [4] have shown that local submucosal infiltration of levobupivacaine is as effective as lidocaine plus epinephrine combination in nasal surgeries for the control of bleeding. Their conclusion was indirectly based on similar perioperative and postoperative hemoglobin and hematocrit values. Although correlation has been previously identified between estimated blood loss and surgical field visualization, Demiraran *et al.* [4] study did not assess the visibility of the surgical field and decongestion or bleeding from mucosa [15].

Pain experienced following FESS is minimal and local anesthesia and preoperative or intraoperative analgesia with paracetamol and cyclooxygenase (COX-2) inhibitors normally provide sufficient analgesia at the end of surgery [9]. When the longer-acting local anesthetic was used, it did not result in a statistically significant reduction in postoperative pain when compared with lidocaine plus epinephrine during the first 24 h after FESS [9,16]. In the present study 15 of 22 patients in levobupivacaine group and 14 of 21 patients lidocaine plus ephinephrine group supplemented analgesia with a single dose acetaminophen during the first 24 h. However, Demiraran *et al.* [4] reported that compared with lidocaine plus epinephrine, levobupivacaine improves postoperative analgesia and reduces the need for supplemental analgesia after nasal surgery. Twelve of 30 (40 %) patients in levobupivacaine group and 18 of 30 (60 %) patients in lidocaine plus ephinephrine group needed rescue

analgesic during the first 24 h in their study and first rescue analgesic time were not evaluated. Our patients needed higher rescue analgesics when comparing to Demiraran *et al.* [4] study. This may be due to intraoperative remifentanil infusion which is known to cause hyperalgesia manifesting as increased postoperative analgesic requirement [17].

As a conclusion, levobupivacaine may be an alternative to lidocaine plus epinephrine because it provides similar surgical visibility and postoperative analgesia in patients undergoing FESS.

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## DISCLOSURE

Work is attributed at Selcuklu Medical Faculty, Selcuk university, Konya, Turkey.

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## CONFLICTS OF INTEREST

None.

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