Original Article

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A prospective randomized trial of xylometazoline drops and epinephrine merocele nasal pack for reducing epistaxis during nasotracheal intubation

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Background: The most frequent complication of nasotracheal intubation (NTI) is epistaxis. Epinephrine nasal gauze packing has been used conventionally as a pre-treatment for reducing epistaxis, but it carries a disadvantage of pain and anxiety in patients. However, xylometazoline drops are easier to administer and more convenient for patients. We aimed at comparing the effectiveness of xylometazoline drops and epinephrine merocele packing in reducing bleeding and postoperative complications in our population.
Methods: Our study enrolled 120 patients in a double-blind randomized controlled trial. We randomly allocated ASA1 or 2 adult patients into 2 groups: Group X and Group E. Group X received 0.1% xylometazoline nasal drops, and epinephrine (1:10,000) merocele nasal packing was used in Group E. The primary outcome was the incidence of bleeding during NTI; the severity of bleeding, navigability, bleeding during extubation, and postoperative complications were secondary outcomes. We used IBM SPSS and Minitab software for statistical analysis, and $P < 0.05$ was considered statistically significant.
Results: We analyzed the data of 110 patients: 55 in Group X and 55 in Group E. The two groups did not have different bleeding incidence (56.4% vs 60.0%; $P = 0.70$); however, the incidence of severe bleeding was less with xylometazoline than with epinephrine (3.63% vs 14.54%; $P < 0.05$). We also observed less bleeding during extubation (38.2% vs 68.5%; $P < 0.05$) with xylometazoline. Other secondary outcomes were akin to both groups.
Conclusion: The incidence of severe and post-extubation bleeding was significantly less with xylometazoline. Hence, it may be an effective alternative for reducing the incidence and severity of epistaxis during NTI.

Keywords: Epistaxis; Nasotracheal Intubation; Xylometazoline.

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INTRODUCTION

Nasotracheal intubation (NTI) is the most common method for securing the airway for maxillofacial and micro-laryngeal surgery; its main advantage is the provision of a good and unobstructed surgical view [1-3]. NTI was mainly popularized by Magill [4] in the 1920s. However, the use of NTI has decreased over time owing to the associated trauma leading to various complications like epistaxis, mucosal damage, and nasal pain [1,5].

Epistaxis is the most frequent complication of NTI, with an incidence as high as 80% [5]. Various pharmacological and non-pharmacological interventions have

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been used to decrease the incidence of epistaxis. The non-pharmacological methods include choosing a more patent nostril, using a smaller size endotracheal tube (ETT), prewarming of the ETT, use of lubricating jelly, and progressively increasing nasopharyngeal airways to dilate the nasal pathway [5-14]. Pre-treatment with vasoconstrictors such as epinephrine and xylometazoline in different formulations have been used as a pharmacological intervention to reduce the incidence and severity of NTI-associated epistaxis.

Seify et al. [5], reported a 7.5% incidence of bleeding with xylometazoline compared with 27.5% in the control group in pediatric dental patients. Song [15] compared the severity of bleeding associated with the use of xylometazoline spray and epinephrine gel, and they found the incidence of no to minimal bleeding to be higher with xylometazoline, while the incidence of moderate bleeding was higher with epinephrine. Owing to the paucity of literature, we aimed to compare the effect of xylometazoline drops and epinephrine merocele packing during NTI. We hypothesized that xylometazoline drops would decrease the incidence and severity of bleeding during NTI better than epinephrine merocele packing.

METHODS

This study was a single-institution double-blind prospective randomized controlled trial. It was approved by the Institutional Ethics Committee with IRB no. INT/IEC/2017/864, and signed written informed consent was obtained from all the participants. The study was registered in the Clinical trial registry of India before the enrollment of the first patient (CTRI/2017/11/010658).

1. Inclusion and exclusion criteria

One hundred and twenty American Society of Anesthesiologists (ASA) grade 1 and 2 patients between 18-60 years of age with normal coagulation profiles scheduled for elective surgeries with durations of < 4 hours were included. The study was conducted from December 2018 to June 2019.

The following patients were excluded: those with a history of (H/O) cough and cold within the past two weeks; those on any oral decongestants, nonsteroidal inflammatory drugs (NSAIDs), or antihistamines; those with h/o nasal deformity or nasal trauma, recurrent epistaxis, any known allergy to study drugs; those with deranged liver function profiles, uncontrolled hypertension; those who were pregnant.

2. Randomization and allocation

Patients were randomized using computer-generated random number tables (www.randomisation.com) and allocated using the sequentially labeled opaque sealed envelope method to one of the two groups. Patients in Group X were administered with 0.1% xylometazoline nasal drops, and epinephrine (1:10,000) merocele packing was used in Group E.

3. Study protocol

In adherence to the institutional protocol, the patients were transferred to the pre-operating room after a thorough pre-anesthetic evaluation, anxiolytic (tablet alprazolam 0.25 mg and tablet ranitidine 150 mcg one day before at night and same day morning) administration, and confirmation of the nil per oral status (solids > 8 h and clear fluids > 2 h).

In group X, the equivalent of 0.6 ml to 3 drops of 0.1% xylometazoline nasal drops were instilled in both nostrils of the patients with their heads tilted backward and in the Mygind's position 30 min before they were transferred to the operating room (OR) [16,17]. In group E, an 8 * 2 * 1.5 cm merocele was inserted in the selected nostril such that it was parallel to the nasal septum along its width and the thread was hanging outside for easy removal afterward. Subsequently, 5 ml of 1:10,000 epinephrine was injected into the merocele so that it uniformly covered the entire nasal cavity. Packing was performed 30 min for all patients in the epinephrine group before their transfer to the OR by a single anesthesiologist who was not involved in the study. This pack was

removed before transfer to the OR.

The anesthesiologist involved in the OR was blinded to both groups. The patient was pre-oxygenated for 3 min and induced with fentanyl 2 mcg/kg and propofol @ 1-2 mg/kg injections in a titrated manner until no response to verbal command. Vecuronium 0.1 mg/kg injection was used to induce muscle relaxation to facilitate NTI, and breathing was supported with manually assisted ventilation. Nostril selection was based on the site of lesion and the surgeon's preference, as it is difficult to choose a better nostril based on preoperative testing [11]. Lidocaine 2% jelly was applied to the selected nostril, and NTI was performed with a 6.5 mm internal diameter (ID)-cuffed Portex® ETT for both male and female patients. If resistance was encountered, the tube was withdrawn and re-inserted with smooth rotational maneuvers and cephalic tilting of the tube. If the tube could still not be navigated successfully, the other nostril was used for intubation; the study sample was taken as a failed attempt. Intubation requiring more than three attempts was considered as failed.

4. Outcomes measured

The incidence of bleeding was the primary outcome of this study. The severity of bleeding during NTI, bleeding during extubation, navigability through the nasal passage, and the level of postoperative patient related to the difficulty in nasal breathing or nasal pain, any nasal trauma, or persistent nasal bleeding were assessed as secondary outcomes.

An independent observer who was not aware of the treatment assignment measured the incidence of bleeding during intubation, and the same observer commented on the severity of bleeding using the four-point rating scale (no bleeding; Mild bleeding- blood only on the tube or cuff of the tube; Moderate bleeding-pooling of blood in the pharynx; Severe bleeding-pooling of blood sufficient to impede intubation and needs vigorous suctioning) [5]. The rating for bleeding was done before the tube crossed the vocal cords.

During NTI, the navigability of the tube through the nasal passage, categorized as smooth or impinged (any subjective feeling of obstruction while passing an ETT), was also documented. Intubation was completed with direct laryngoscopy with the help of Magill forceps. The anesthesiologist performing the intubation commented on the navigability of the tube and bleeding on the cuff, if any, before the tube was passed through the vocal cords.

5. Anesthesia protocol

Anesthesia was maintained with volatile anesthetics (isoflurane), nitrous oxide, and oxygen (50:50), to keep minimum alveolar concentration (MAC) at approximately 1-1.2. Ventilation was adjusted to maintain end-tidal carbon dioxide (ETCO2) between 35 and 40 mmHg. All patients were monitored with standard monitoring procedures: pulse oximetry; electrocardiography (ECG); non-invasive blood pressure (NIBP); inspiratory and expiratory O2, N2O, and ETCO2; peak and plateau airway pressure monitoring. At the end of the procedure, the administration of the anesthetic agents was discontinued, replaced with 100% O2. The ETT was removed smoothly by the same anesthesiologist who had performed intubation after fulfilling the criteria of extubation and observing any traces of bleeding on the cuff. Before discharging a patient from the post-anesthesia care unit (PACU), subjects were checked for any nasal trauma or persistent nasal bleeding and asked for any difficulty with nasal breathing or nasal pain.

6. Statistical analysis

Assuming a reduction of bleeding from 33% to 10% by our intervention, an α of 0.05, and a β of 0.2, we considered a sample size of 60 per group, with necessary considerations for attrition. The data collected were presented as mean (± SD), median (range), frequencies (number of cases), and percentages, where appropriate. The normality of the data was tested using the appropriate test (Kolmogorov–Smirnov or Shapiro-Wilk test). The unpaired t-test (normality assumption met) or Wilcoxon rank or Mann-Whitney test (normality assumption not met) was used to compare the two groups. Pearson's

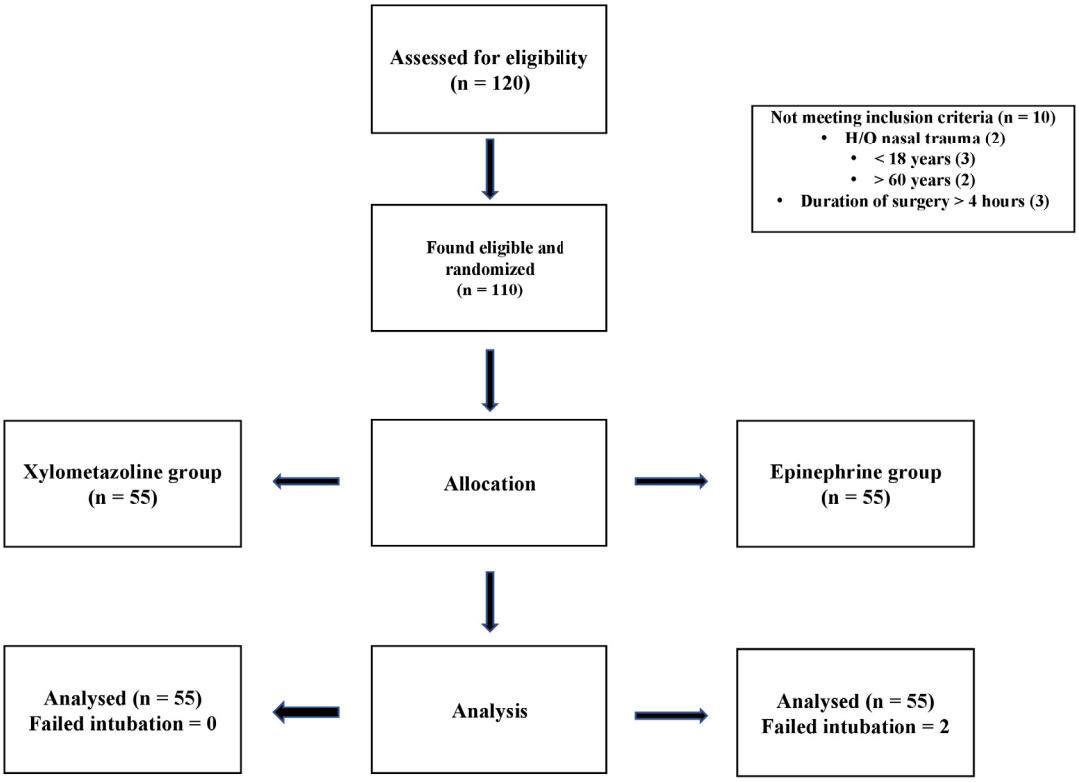

Fig. 1. CONSORT chart depicting recruitment

Table 1. Patient baseline characteristics

Variables	Group X (n = 55)	Group E (n = 55)	P-value
Age (years)	34.291 ± 14.90	36.055 ± 14.62	0.349*
Weight (kg)	66.000 ± 12.05	67.055 ± 11.87	0.555*
Sex (n [%])			
Male	46 (83.6%)	45 (81.8%)	0.801†
Female	9 (16.4%)	10 (18.2%)	
ASA (n [%])			
1	46 (83.6%)	39 (70.9%)	0.111†
2	9 (16.4%)	16 (29.1%)	

*Compared using independent sample student's t-test.
†Compared using Pearson's chi-square test.
P-value < 0.05 was considered as statistically significant.
ASA, American Society of Anaesthesiologists.

chi-squared test (x^2 test) or Fisher's exact test was used to assess the association or independence of the qualitative variables of the groups. A $P < 0.05$ was considered statistically significant. The statistical analysis was carried out using IBM SPSS (Statistical Package for Social Sciences) version 20 and Minitab software.

RESULTS

Of the 120 patients were recruited, 10 patients were excluded. Fig. 1 shows the CONSORT diagram of patient recruitment, randomization, and analysis.

Patient characteristic data, number of intubation attempts, navigability, and nostril selection in the groups

Table 2. Intubation characteristics

	Group X (n = 55)	Group E (n = 55)	P-value
Number of attempts n (%)			
1	54 (98.2%)	49 (89.1%)	0.073*
2	1 (1.8%)	1 (1.8%)	
3	0 (0.0%)	5 (9.1%)	
Navigability			
Smooth	44 (80%)	32 (60.3%)	0.071*
Impinged	11 (20.0%)	23 (39.7%)	
Nostril (n [%])			
Right	36 (66.5%)	34 (61.8%)	0.692*
Left	19 (34.5%)	21 (38.2%)	
Failed nasal intubation (n [%])*	0	2	

*Compared using Pearson's chi-squared test. P < 0.05 was considered as statistically significant.

Table 3. Incidence and severity of epistaxis in nasotracheal intubation (NTI)

Epistaxis N (%)	Group X (N = 55)	Group E (N = 55)	P-value*
Bleeding	31 (56.4%)	33 (60.0%)	0.700
Severity			
No	24 (43.6%)	22 (40.0%)	0.169
Mild	24 (43.63%)	17 (30.90%)	0.169
Moderate	5 (9.09%)	8 (14.54%)	0.381
Severe	2 (3.63%)	8 (14.54%)	0.048

*Compared using Pearson's chi-squared test. P < 0.05 was considered as statistically significant.

showed no significant differences (Table 1, 2).

1. Incidence and severity of epistaxis

Table 3 shows the incidence and severity of bleeding during the NTI. There was no statistically significant difference in the overall incidence of bleeding in the two groups (60% vs 56.4%; P = 0.700).

On comparing the severity of bleeding in both groups, there was no significant difference in the incidence of mild bleeding (43.63% vs 30.9%; P = 0.169) and moderate bleeding (14.54% vs 9.09%; P = 0.381). However, a significantly higher incidence of severe bleeding was noted in patients in the epinephrine group (8 [14.54%]) compared to the xylometazoline group (2 [3.63%]; P = 0.048).

2. Post-operative complications

Post-extubation bleeding was significantly high in the epinephrine group (68.5%) than in the xylometazoline group (38.2%; P < 0.005). Difficulty in nasal breathing was noted in 1 patient in the epinephrine group whereas 2 patients in the xylometazoline group complained of nasal stuffiness. None of the patients had nasal pain, blood crusts, or mucosal tearing (Table 4).

Table 4. Post-operative complications

Complications	Group X (n = 55)	Group E (n = 55)	P-value
Post extubation bleeding			
No	34 (61.8%)	17 (31.5%)	0.002*
Yes	21 (38.2%)	37 (68.5%)	
Postoperative complications			
Difficulty in nasal breathing,	0	1 (1.9%)	0.261*
Nasal stuffiness	2 (3.6%)	0	

*Compared using Pearson's chi-squared test. P < 0.05 was considered as statistically significant.

Table 5. Division of surgical department

Surgery	Group X	Group E	P-value
Dental surgery	7 (12.7%)	7 (12.7%)	0.012*
ENT	22 (40.0%)	8 (14.5%)	
Plastic surgery	25 (45.5%)	40 (72.7%)	
Urology	1 (1.8%)	0 (0.0%)	

*Compared using Pearson's chi-squared test. P < 0.05 was considered as statistically significant

Nasotracheal intubation was mainly performed in four surgical specialties during our study, and plastic surgery dominated in both the groups (Table 5).

DISCUSSION

The results of our study demonstrated a significantly higher incidence of severe bleeding with epinephrine merocele packing during the procedure and post-xtubation than with xylometazoline drops. However, there was no difference in the overall, mild, and moderate bleeding as well as postoperative nasal pain or mucosal damage in the two groups.

In the present study, two commonly available vaso-constrictors, xylometazoline and epinephrine, were studied during NTI. Both are non-selective directly acting adrenergic agonists, while xylometazoline acts on α-drenergic receptors; epinephrine acts on both α and β

receptors [18]. Local vasoconstriction following topical application is mainly attributed to their α-agonist activities. Xylometazoline has an onset duration of 5-10 min and duration of action of 6-8 h [19], while the onset of action for vasoconstriction following topical epinephrine administration is 5 min and the duration of action is approximately 1 h.

Epistaxis during NTI does not only obscure the surgical field; it also threatens the airway patency. Other complications of NTI include nasal trauma, nasal pain, and difficulty breathing, and all these complications may unnecessarily increase morbidity or even lead to mortality.

Various techniques like thermos-softening of ETT by dipping in sterile warm saline, the application of lidocaine jelly, siliconized nasopharyngeal airway, and gradual dilatation with increasing size of ETT are used in our institution to prevent epistaxis. As it was difficult to maintain a uniform temperature for thermo-softening, we preferred to use 2% lidocaine jelly in both groups along with the study drugs in our trial.

We used 6.5 mm ETT for both males and females, although most of the studies used 6.5 mm ETT for females and 7.0-7.5 mm for males [15,20]. This was based on a previous study suggesting that the minimum cross-sectional area and nasal volume are not significantly different in males and females [21].

The overall incidence of bleeding in patients pre- reated with xylometazoline nasal drops and epinephrine was 56.4% and 60%, respectively. The incidence of bleeding in the epinephrine group was consistent with the findings of a previous study by Katz et al. [22], who reported a 71% incidence of bleeding with lidocaine-epinephrine. The incidence of bleeding was much higher; 56% in the xylometazoline group compared to 7.5%, as reported by Seify et al. [5]. The latter had used a soft siliconized tube, which has been shown to decrease the incidence of epistaxis during nasal intubation, in contrast to the PVC tubes used in our study [23]. Other possible reasons for this difference include the difference in age, the race of the study population, and the experience of the person performing the procedure.

The incidence of bleeding is important; the grading of its severity is also important. In our study, we graded the severity of bleeding using a 4-point scale [5]. No significant difference was observed in the incidence of mild and moderate bleeding in the two groups in our study. In contrast to our study, some adult studies did not report the incidence of minimal bleeding independently; they reported it together with "none" as none to minimal bleeding. Song [15] reported an incidence of 85% for mild to no bleeding. With this data, it is difficult to interpret how many of the patients had mild bleeding. As the majority of our patients had mild bleeding, direct comparisons with previous studies involving adult studies may not be possible.

In our study, the incidence of severe bleeding was 14.54% in Group E and 3.63% in Group X, which was statistically significant ($P = 0.048$); Song [15] had no incidence of severe bleeding. This could be due to the use of the Polar^{TM} Preformed Tracheal Tube by the latter as the ivory-colored PVC tube is much softer than a regular PVC tube, which was used in our study.

The rate of smooth intubation was higher in the xylometazoline group (80%) than in the epinephrine group (60.3%). This was similar to another study that reported that the rate of smooth intubation with xylometazoline was 75% compared to 65% with epinephrine [15].

During and after extubation, several complications such as persistent bleeding, nasal stuffiness, difficulty nasal breathing, nasal pain, or nasal trauma may occur. A significant incidence of post-extubation bleeding was observed in the epinephrine group (68.5% compared to 38.2% with xylometazoline; $P < 0.005$). The high incidence of post-extubation bleeding with epinephrine can be attributed to "after congestion", which can be observed with locally applied epinephrine after vasoconstriction owing to its comparatively short duration of action of 1 hour compared to the 6-8 h duration of xylometazoline [18]. Seify et al. [5] also observed a higher incidence of post-extubation bleeding in the control group than in the xylometazoline group (21.6% vs 3.8%).

Although gauze or cotton swab packing is conventionally and commonly used, we preferred using merocele packing in our study, as a uniform drug distribution across the NTI route cannot be guaranteed with cotton swab packing. Moreover, it can lead to more mucosal damage and epistaxis if it is performed by an untrained person [15]. On the other hand, a merocele pack is easier to insert, and it ensures uniform drug distribution as its length covers the entire nasal cavity. Studies that used nasal packing with cotton swab have reported that it is a painful technique to the extent that some patients refused cooperation [15,24]. No study has compared the pain associated with cotton swab and merocele packing.

Merocele packing was painful, and all the patients were psychologically prepared through counseling. Although some studies have used lignocaine spray to decrease pain before pack removal after intranasal surgery [25], the use of lignocaine spray before packing for nasal intubation remains unevaluated. We did not use lidocaine spray before packing, as the residual moisture in the nasal cavity after the spray could have hindered the insertion of the complete length of the merocele, as it tends to swell after contact with moisture. We inserted the merocele before anesthesia to make our study double-blind.

Apart from being painful, merocele packing is also more expensive, and it has a higher risk of nasal mucosal damage than xylometazoline nasal drops. However, in our study, we did not observe mucosal damage in any patient. Despite these shortcomings, it has advantages such as easy insertion and removal and uniform drug distribution to the entire nasal cavity.

The importance of head positions during the instillation of nasal drops has also been described in the literature [16,17]. We combined two head positions: the backward tilt of the head, where drugs administered through nasal drops flow into the inferior meatus and nasopharynx; the Mygind's position, in which the instilled nasal drops mainly go to the middle meatus. Combining both positions gave the added advantage of covering the middle and inferior meatus to further reduce the incidence of epistaxis; however, both positions could only be used in the xylometazoline group.

Our study had several limitations. Firstly, we did not include the placebo control group as it was considered unethical. Secondly, we did not investigate the nasal pathway and the duration of resistance owing to the limited availability of the fiberoptic bronchoscope for evaluation. The total duration of intubation, which could influence the bleeding during NTI, was not recorded; however, intubation was considered as unsuccessful if > 3 attempts were made. Thirdly, the method of bleeding assessment was subjective, as it was dependent on the anesthesiologist intubating the patient, but we tried to improve the validity of the method by standardizing the independent observer for all subjects and reassessing the external bleeding post-extubation. Fourth, only ASA 1 and ASA 2 patients were included in the study. Fifth, we did not follow-up for the hospital discharge time, and we could not determine if it was affected by our method, but the duration of hospitalization depends on several factors.

In conclusion, pre-treatment with xylometazoline nasal drops results in a lower incidence of severe and post-extubation bleeding during NTI. It also has additional advantages of convenience, availability, patient comfort, and a lesser chance of drug error, and it is a superior option to epinephrine merocele pack during NTI.

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Amarjyoti Hazarika: Conceptualization, Formal analysis, Project administration, Supervision, Writing - review & editing
Prachi Agrawal: Data curation, Resources, Writing - review & editing
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