JOURNAL of ANESTHESIA and PERIOPERATIVE MEDICINE

Original Article

Effect of Intra-Cuff Tetracaine on Preventing Postoperative Sore Throat after Gynecological Surgery

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Citation: Qing Zhu, Hai Wu, Hai- Bo Song, Ting Liu, Bei Liu, Chun- Lan Zheng, et al. Effect of intra-cuff tetracaine on preventing postoperative sore throat after gynecological surgery. *J Anesth Perioper Med* 2015; 2: 8-13.

ABSTRACT

Background: Postoperative sore throat is one of the most common complications associated with endotracheal intubation. It has been reported that intra-cuff application of lidocaine could reduce its incidence and severity. In the present study, we would like to investigate the safety and efficacy of intra- cuff use of tetracaine, one of the most commonly used topical anesthetic, on prevention of postoperative sore throat.

Methods: Female patients (age from 18-60 years) undergoing gynecological surgery under general anesthesia were included. Assigned randomly, the patients received one of the following cuff inflation media: air, 0.9% saline, 2% lidocaine or 1% tetracaine (N=25 in each group). The cuff was inflated with minimal occlusive volume technique. Intra- cuff pressure was measured with a manometer. The primary outcome was the severity of postoperative sore throat, assessed by visual analogue scale (VAS) at 6 hours after extubation. The secondary outcomes included the incidences of complications during emergence of anesthesia and extubation, such as tube intolerance, coughing, restlessness, hoarseness, and laryngospasm, as well as the VAS scores for sore throat at 24 and 48 hours after extubation. The safety and efficacy were further tested by pathological examination of tracheal mucosa after 4-hour intubation in animal study and measurement of diffused anesthetic via the cuff wall in in vitro study, respectively.

Results: There was no difference in volume of inflation medium, or intra-cuff pressure between groups. Tetracaine significantly reduced the severity of postoperative sore throat during the 48-hour postoperative observation period, compared with lidocaine ($P<0.05$) or air ($P<0.01$). There were also fewer patients with tube intolerance, coughing, restlessness and hoarseness in tetracaine group, compared with lidocaine group ($P<0.05$) or air group ($P<0.01$). No abnormality was found in tracheal mucosa pathology and tetracaine diffused via the cuff wall continuously.

Conclusions: Our study showed that inflating the cuff with tetraciane is safe and effective in preventing tube-induced emergence phenomena.

Endotracheal intubation has become a standard care in contemporary anesthesia practice. Prevention of tube-induced emergence phenomena, such as sore throat, cough, or hoarseness, remains a challenge for anesthesiologists (1-3). For example, the incidence of postoperative sore throat could be as high as 40% in general population (4- 7) and is even higher in female patients (4). It is believed that tube- induced emergence phenomena mainly result from traumatic mucosal injury during intubation and extubation (8, 9). Local anesthetics could be used to block these nociceptive stimuli (10) and intravenous administration or

forestalling local spray of lidocaine has been proved useful in preventing sore throat during emergence (11-13). Previous studies further indicated that endotracheal tube (ETT) cuff could serve as a reservoir for lidocaine, allowing lidocaine to diffuse across the cuff to prevent ETT-induced emergence phenomena (14-18).

Tetracaine has been widely used for topical anesthesia. Therefore, intra-cuff application of tetracaine may also prevent ETT-induced emergence phenomena. Based on this assumption, we designed this prospective randomized trial to investigate the effect of inflated ETT cuff with tetracaine on postoperative sore throat in high risk populations, i.e. the gynecological patients. The safety and efficacy of this strategy were further tested in animal study and in vitro study.

METHODS

Clinical Trial

This randomized, controlled and double-blinded clinical trial was approved by our Institutional Ethics Committee. Patients undergoing gynecological procedures under general anesthesia with endotracheal intubation were recruited, and informed consents were obtained. They were aged 18-60 years old with the American Society of Anesthesiologists (ASA) physical status class I to II. Exclusion criteria included: 1) previous history of oral, pharyngeal, cervical spinal or thyroid surgery; 2) previous history of symptomatic gastric reflux, postoperative sore throat, pulmonary disease, or allergy to any local anesthetics; 3) previous history of or suspected difficult airway; 4) a nasogastric tube needed for postoperative management; 5) upper respiratory tract infection in the last month; and 6) smoking.

Totally 104 patients were screened and 4 patients refused to participate. Therefore, 100 patients were finally included. According to a computer-generated random number table, they were assigned to receive one of the following media to inflate the cuffs of the endotracheal tubes: 1% tetracaine (Group T, N=25), 2% lidocaine (Group L, N=25), 0.9% normal saline (Group N, N=25) or air (Group A, N=25).

A standard protocol was used for anesthesia induction: midazolam 0.05 mg/kg, fentanyl 4 μg/kg, propofol 2 mg/kg. Tracheal intubation was facilitated by rocuronium 0.6 mg/kg or vecuronium 0.1 mg/kg. Endotracheal intubation tubes with low-pressure and high-volume cuffs (Medical Devices Co., Ltd. Guangzhou peacekeeping force, Guangzhou, China) were used in this study. The size of the tube for each patient was determined by the attending anesthesiologist assigned for each case and intubations were performed by anesthesiologists who had more than 3 years of practicing experience and were blinded to group allocation. Stylet for endotracheal intubation was used in every subject. According to the randomization table, all the endotracheal tubes and the corresponding inflation media were freshly prepared by the same nurse anesthetist who was not involved in intraoperative anesthesia management or postoperative follow-up. The cuff of the ETT was slowly inflated with the assigned inflation medium to occlude the leak around the tube by the minimal occlusive volume technique. Briefly, a small volume of inflation medium was injected into the cuff by the same nurse anesthetist, until no leak was heard during the peak airway pressure of the ventilation cycle by the anesthesiologist in charge of each patient. The volume of injected inflation medium was recorded and intra-cuff pressure was measured with a manometer. During this process, the cuff and the connected syringe or manometer were covered by black paper, which made them invisible to anesthesiologist in charge. The anesthesia maintenance was performed at the discretion of the anesthesiologist in charge of each patient, either with sevoflurane inhalation or propofol infusion. Depolarizing muscle relaxants or long-acting opioids, such as sufentanil, were avoided.

The deliveries of anesthetics would be stopped after the final stitch was completed. Once the extubation criteria were met (adequate spontaneous ventilation and response to verbal command to open her eyes), ETT would be removed.

The postoperative follow-ups were conducted by certified registered nurse anesthetists blinded to the randomization. The primary outcome was the severity of the post-intubation sore throat measured by the Visual Analogue Scale (VAS) score at 6 hours after extubation. The secondary outcomes were incidences of ETT-induced emergence phenomena, which were defined as com-

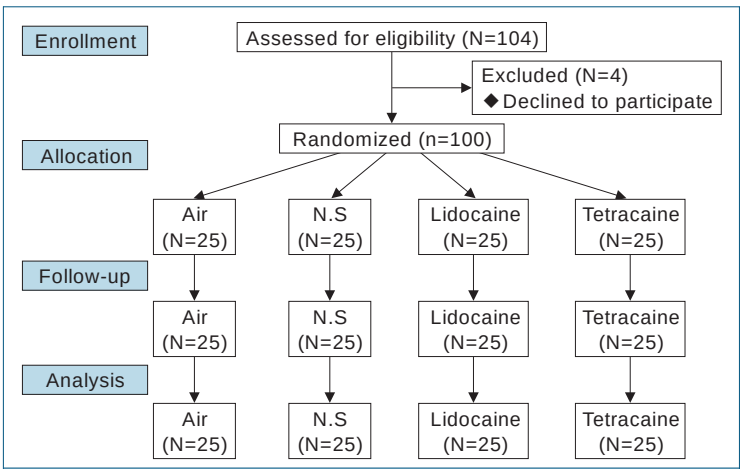

Figure 1. The Flow Diagram of the Clinical Trial.

plications related to endotracheal intubation including tube intolerance, coughing on tube, restlessness, hoarseness, and laryngospasm, as well as the VAS scores at 24 and 48 hours after extubation. Duration of intubation was also recorded. The flow chart was presented as figure 1.

In Vitro Study

For the in vitro test, ID 6.5 mm tubes with low-pressure and high-volume cuffs (Medical Devices Co., Ltd. Guangzhou peacekeeping force, Guangzhou, China) were prepared and divided into two groups. 1% tetracaine and 2% lidocaine was used to inflate the cuff, respectively. The intra-cuff pressure was set at 14 mm Hg, guided by the results from our human study. Each ETT was then placed in a magnetically stirred bath of 100 ml normal saline at 37℃. Samples (1 ml) of the bath contents were drawn every 30 minutes for 300 minutes. The concentration of local anesthetic in the samples was measured by High Perform Liquid Chromatography (Agilent 4860, Santa Clara, CA, USA), according to our well established protocol. This diffusion test would be repeated for 5 times for each local anesthetic.

Animal Study

The animal study was approved by our institutional Animal Experimental Ethics Committee. Dogs were anesthetized with intramuscular (i.m.) injection of 5 mg/kg ketamine. Then peripheral vein was catheterized. 0.1 mg/kg midazolam, 0.05 μg/kg sufentanil and 2.5 mg/kg propofol were given and tracheal intubation was facilitated with rocuronium at the dose of 0.6 mg/kg. At this stage, the dogs were divided into 2 groups (N=6 per group) randomly, according to the type of media received for inflating the ETT cuff (normal saline or air). The cuff was inflated by minimal occlusive volume technique as previously described, and the intra-cuff pressure was also measured by manometer. The dogs were kept in supine position during the 4-hour intubation and anesthesia was maintained by continuous midazolam and remifentanil infusion. After the tube was removed, the trachea underneath the cuff was harvested for pathological investigation by a trained pathologist. The lesions of the trachea were scored according to severity and distribution (19). Scores for severity were: none=0, minimal=1, mild=2, moderate=3, marked=4 and severe=5. Scores for distribution were: none=0, focal=1, locally extensive=2, multifocal=3, multifocal and coalescent=4 and diffused=5. The pathology score was the sum of the severity and distribution scores.

Statistics

Power calculation for the human study was based on our preliminary data. A minimum of 90 patients had to be included to detect a 2-point decrease in VAS with a two-sided significance level of 0.05 and power of 80%. Considering potential loss during follow-up, sample size of 25 for each group was determined.

Data analysis was performed using Graphpad Prsim Software (version 5.01, GraphPad Software, Inc., La Jolla, CA, USA). Quantitative data between groups were analyzed by one-way analysis of variance (ANOVA) test, followed by Student-Neumann-Keuls test when indicated, except for age. Age was analyzed by Kruskal-Wallis test, followed by Nemenyi test when necessary. VAS score for sore throat was analyzed by the Kruskal-Wallis test, followed by the Mann-Whitney U test when indicated at each time point. The incidences of intubation-related complications were compared by the Pearson Chi-square test. All the reported P values were two-tailed and P value less than 0.05 was considered statistically significant.

RESULTS

A total of 104 patients were recruited and 4 pa-

Table 1. Demographics.

	Air (A)	Tetracaine (T)	Lidocaine (L)	N.S (N)	P
Age (year)	39 (25-48)	40 (19-56)	45 (23-57)	46 (21-59)	0.5398
Weight (kg)	54.7±3.55	51.7±7.4	49.5±6.2	49.2±5.8	0.6248
Height (cm)	156.0±9.1	149.5±8.9	149.6±7.7	151.4±7.1	0.1579
Duration of surgey (minute)	137.8±45.2	129.3±43.9	138.5±66.8	119.0±38.5	0.3279
Duration of intubation (minute)	165.7±54.2	167.6±53.0	165.6±56.1	144.6±47.2	0.7856
Volume of inflation medium (ml)	3.4±0.5	3.6±0.5	3.6±0.5	3.8±0.4	0.3584
Intra-cuff pressure (mm Hg)	15.4±3.2	14.2±3.3	14.0±3.2	13.6±2.6	0.5492
Mallampati score I	13	10	11	14	0.6591
Mallampati score II	12	15	14	11	
Intubation attempt	1	1	1	1	

There was no difference in demographics or surgical profiles between the four groups. Age is presented as mean (range); weight, height, duration of surgery, duration of intubation, volume of inflation medium and intra-cuff pressure were presented as means±SD.

tients refused to participate. Totally 100 patients were included for analysis. Patient characteristics and duration of surgery were comparable between the groups. There was no difference in duration of surgery or intubation, the volume of inflation medium, or intra- cuff pressure between groups. All the patients had Mallampati score≤II. All the patients were successfully intubated with ID 6.5 mm ETT at the first attempt (Table 1).

As shown in table 2, the severity of post-intubation sore throat was significantly reduced in patients receiving tetracaine as inflation medium, compared with patients receiving other inflation media ($P<0.05$), at 6 (primary outcome), 24 and 48 (secondary outcomes) hours after extubation. As previously reported (20), lidocaine, per se, could reduce sore throat when compared with normal saline or air ($P<0.05$).

Similarly, the incidences of tube intolerance, coughing on tube, restlessness and hoarseness were least in the tetracaine group. Compared with normal saline and air groups, lidocaine group had the significantly decreased incidences of ETT-induced emergence phenomena (Table 3).

With our in vitro study, we demonstrated that both lidocaine and tetracaine could diffuse through the cuff continuously. However, the diffusion rate seemed more stable with tetracaine (Figure 2).

The intra- cuff pressure was comparable between dogs receiving air as inflation medium and dogs receiving normal saline (13.8 ± 2.8 versus 14.6 ± 2.9 mm Hg). No abnormality was found in the tracheal pathology examination and there was no difference in pathology score between these two groups (Figure 3).

Table 2. Visual Analogue Scale (VAS) Score of Sore Throat.

	6 hours	12 hours	24 hours	48 hours
Tetracaine (T)	9 (5-30)*#	13 (10-35)*#	7 (5-20)*#	9 (5-15)*#
Lidocaine (L)	22 (10-35)+	25 (15-45)+	20 (15-30)+	25 (15-50)+
N.S (N)	40 (30-60)	38 (25-90)	41 (30-90)	43 (25-80)
Air (A)	51 (35-70)	50 (25-85)	43 (35-90)	45 (35-75)

The VAS scores of sore throat are presented as medians (ranges).
*P<0.05 Tetracaine group versus lidocaine group;
#P<0.01 Tetracaine group versus N.S group or air group;
+P<0.05 Lidocaine group versus N.S group or air group.

Table 3. The Incidences of Other Intubation-Related Complications.

	Tetracaine	Lidocaine	N.S	Air	P
Coughing on tube	3 (12%)#	8 (32%)*	19 (76%)	20 (80%)	<0.001
Restlessness	1 (4%)	3 (12%)*	8 (32%)	8 (32%)	<0.05
Hoarseness	4 (16%)#	9 (36%)*	18 (72%)	19 (76)	<0.001
Laryngospasm	0 (0%)	0 (0%)	0 (0%)	0 (0%)	>0.05

Values are presented as number of patients (percentage).
*Lidocaine reduced the incidences of intubation- related complications when compared with normal saline or air (P<0.05).
#Tetracaine further reduced incidences of intubation- related complications when compared with lidocaine (P<0.05).

DISCUSSION

This study demonstrated that inflation of ETT cuff with tetracaine could prevent ETT- induced emergence phenomena in gynecological surgery. The animal study further confirmed that the safety of intra-cuff application of tetracaine, while in vitro assay provided further evidence on the efficiency of intra-cuff application of tetracaine.

Sore throat is one of the common complications in gynecological patients (21) and has been referred as one of the ETT- induced emergence phenomena (22). Even with a "gentle" intubation, the complication still occurs. Although

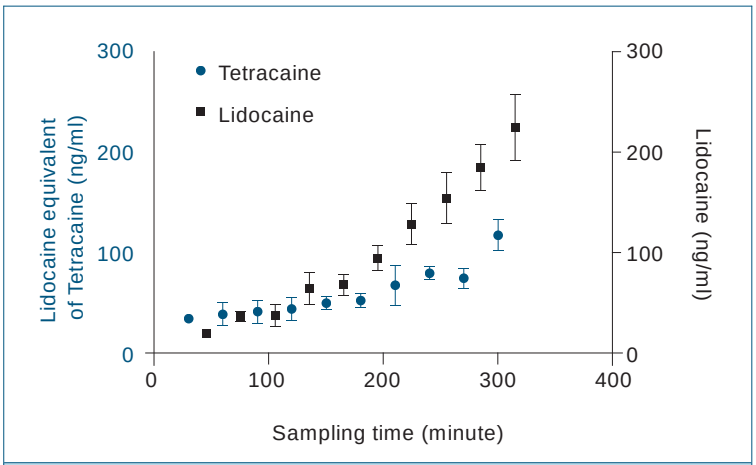

Figure 2. The diffusion of tetracaine and lidocaine through the cuff wall.
Both anesthetics diffused effectively through the cuff. However, the diffusion of tetracaine was more stable as time elapsed.

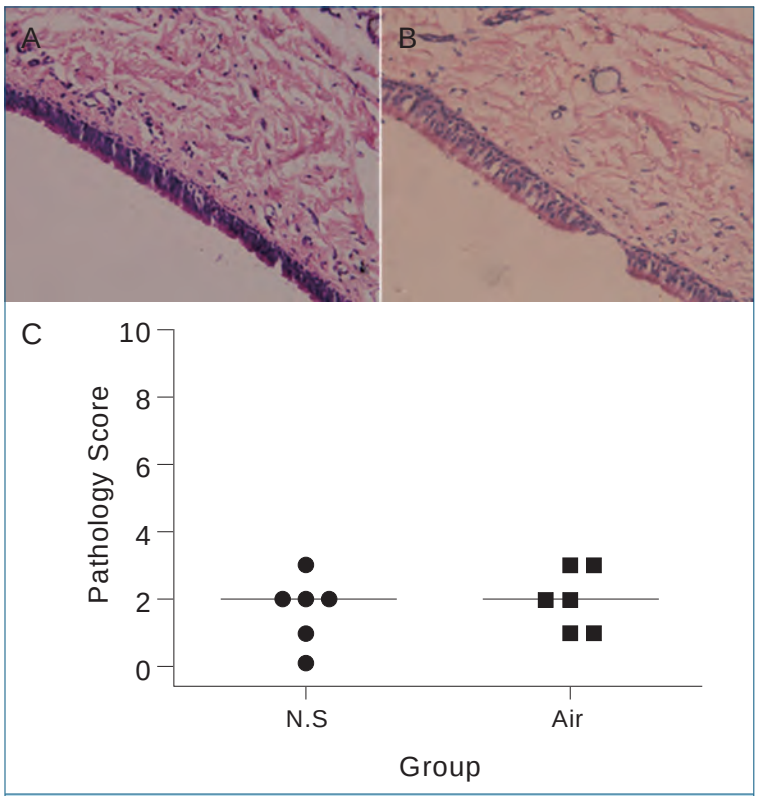

Figure 3. Tracheal pathology.
The mucosa was intact and no abnormal pathology was noted in either group. A. Representative figure from animals receiving normal saline; B. Representative figure from animals receiving air (magnification X 200); C. No difference in tracheal pathology was detected between animals receiving normal saline and air as cuff inflation medium. The bar indicated the median of the tracheal pathology scores.

these symptoms could resolve spontaneously and require little treatment, they still assert huge impact on patients' hospital experience and satisfaction. Therefore, prophylactic strategies for decreasing sore throat frequency and severity are still recommended. It's self-evident that the complication primarily resulted from the irritation of tracheal mucosal receptors (23, 24), which might lead to further local inflammation or/and edema (25). Therefore, blocking these receptors with local anesthetics, such as lidocaine, should be an effective option for preventing ETT-induced sore throat, as demonstrated by previous studies (12, 13).

Tetracaine has been well known for producing potent and long-lasting topical anesthesia. In a previous study, the authors demonstrated that tetracaine is superior to lidocaine in providing topical anesthesia for nasal procedures (26). According to the results of previous studies (11, 12), the highest incidence of sore throat occurred at 6 hours after extubation. So our primary outcome should especially focus on the severity of postoperative sore throat at 6 hours after extubation. Our data confirmed that the use of tetracaine into the ETT cuff offered the advantages of minimal sore throat at 6 hours after smooth tracheal extubation. Furthermore, during the 48-hour postoperative observation period, we proved that tetracaine provided better topical anesthesia in tracheal mucosa, as evidenced by decreased severity of sore throat and incidences of other ETT-induced emergence phenomena, such as tube intolerance, coughing, restlessness and hoarseness.

It was not surprising that both lidocaine and tetracaine diffused through the cuff wall and it was reasonable for us to believe that the diffused local anesthetics played a vital role in the prevention of ETT-induced emergence phenomena. In the present study we further demonstrated that the amount of diffused tetracaine was comparable to the diffused lidocaine, which was 4 times less potent as well accepted. The stable diffusion rate of tetracaine also minimized the systematic accumulation of diffused tetracaine after long-term intubation. Future studies should focus on confirming these in vitro results in patients.

One important reason for much less use of tetracaine for topical anesthesia was its toxicity. There have been some case reports, in most of which the dose of tetracaine was larger than 100

mg (27). In our study, the volume for cuff inflation was no more than 5 ml and the dose of tetracaine was less than 50 mg, which was much less than the toxic dose. Therefore, even with unexpected cuff rupture, the released tetracaine would cause no adverse events. With further studies identifying the dose-response curve, the dose of tetracaine might be further reduced without reducing the efficacy.

Another approach to reduce ETT- induced emergence phenomena was to use alkalinized lidocaine as the inflation medium, as advocated by some researchers (17, 18, 28). It is not clear yet, when compared with tetracaine used in the present study, which one would be more effective. But there was at least one advantage of tetracaine, i.e. the preparation of alkalinized lidocaine was clearly much more complicated than that of tetracaine alone.

One concern for using liquid inflation was that the weight of the inflation liquid might cause direct injury to the fragile tracheal mucosa, especially after a long-term inflation. However, our data showed that no subject had any complication resulting from severe mucosa injury, and the animal study revealed no abnormal pathology (Figure 3). This concern could be greatly relieved.

CONCLUSION

In conclusion, our study demonstrated that the application of 1% tetracaine as the cuff inflation medium could effectively decrease the incidences and severity of intubation-related complications, compared with 2% lidocaine, 0.9% normal saline or air. The dose of tetracaine used for cuff inflation was much less than that would cause systematic toxicity. Therefore the use of tetracaine to inflate the cuff is an easy and safe practice.

This study was partially supported by the National Nature Science Foundation of China (No. 30772084 and No. 81401623).

No other conflicts of interest declared.

Part results of this study were presented at the 2009 ASA annual meeting.

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