

Egyptian Journal of Medical Research (EJMR)



Comparison Between Blind And Ultrasound Guided Laryngeal Mask Airway

Insertion In Adult Patients Undergoing Elective Surgery: A Randomized Control Study

Ahmed Mostafa El-Shaarawy^a, Mohamed Abdelrahman Moselhy^b, Dina Mohamed Nour El-Din^c.

Anesthesiology, Surgical ICU and Pain Department, Faculty of Medicine, Beni-Suef University,

Egypt

Abstract

The goal of this study is to compare between the blind technique and US guided technique in insertion of the LMA and confirming its position. A 102 patients who underwent elective surgery were randomly selected and grouped into 2 groups, 51 in each group. Group B: using the blind technique in positioning of the LMA and confirming its position by the fiberoptic score and group U: using the US in positioning the LMA and confirming its position by the fiberoptic score The laryngeal mask insertion time for 1st group was significantly shorter than that for the 2nd group. The fiberoptic glottic view scores for 2nd group was significantly better than that for the ones for 1st group. The side effects and complications had no statistical difference between the two groups.

Keywords: laryngeal mask airway, ultra sound, fiberoptic

1. Introduction:

The laryngeal mask airway (LMA) is a useful device for airway management at some stage in anesthesia which has been invented by way of Dr. Arch Brain in 1981. It is favored for its easy insertion and lesser impact on cardiovascular balance for the duration of general anesthesia. (1)

The Proper function of a laryngeal mask airway (LMA) requires confirmation to make certain the adequacy of laryngeal seal and pulmonary ventilation. This affirmation may additionally assist in prevention of the peri-operative airway difficulty and air flow events associated with LMA placement. (2)

Successful insertion is typically assessed clinically with a capnogram, appropriate chest excursion, and the absence of an audible leak at a peak inspiratory pressure of 20 cm H2O. However, even though all of those clinical signs are reassuring, one cannot be certain that correct positioning has been achieved. Fiberoptic bronchoscope (FOB) research have shown that despite the fact that ventilation can judged adequate, be as а suboptimal anatomical positioning with partial or

complete obstruction of the view of the glottis apertures might also occur, (3) this outcomes additionally showed by the MRI study. (4) .

A common practice is to inflate the cuff with the maximum encouraged volume (length 3, 20 ml; length 4, 30 ml; size 5, 40 ml), as illustrated in several research (5), but it may turn out to be more rigid which may additionally cause displacement of the LMA and reduces the airway sealing of LMA(6), more strain on pharyngeal mucosa which might purpose extreme mucosal ischemia leading to post- operative sore throat,

dysphagia or hoarseness.(7)

Ultrasonography can reliably confirm correct placement of supraglottic devices like laryngeal mask airway (LMA) and guidelines out causes of insufficient ventilation (2), also it was discovered to be a sensitive in detecting rotational malposition of LMA in children. (8) Wojtczak et al. Demonstrates that the alternative of air with saline in LMA cuffs enable detection of cuffs within the airway allowing visualization of the encompassing structures and tissues as the ultrasound beam may be transmitted via the flui - crammed cuffs without being contemplated from air mucosal interface. (10)

Campbell et al. Concluded that a fiberoptic laryngoscope (FOL) acts as one among affirmation tool that assesses the adequacy of LMA position. (11)

2. Patients and Methods:

This was a randomized study performed in Beni-Suef university hospital within six months from August to February 2020 involving 102 patients. Written consents were obtained.

2.1 Inclusion criteria:

Patients aged from 18- 60 years of either sex, ASA physical status I – II, weighting 50-100 kg, who were scheduled for elective surgery under general anaesthesia.

2.2 Exclusion criteria:

1. Patients whom LMA is contraindicated as patients who are at an increased risk of gastric aspiration as (obstetrics, hiatal hernia or esophageal reflux), patients with high airway resistance e.g. (bronchospasm or pulmonary edema), patients with low pulmonary compliance e.g. (obesity), cases of an inability to open the mouth or an infection or pathologic abnormality within the oral cavity or pharynx and non supine position of operation.

2. Patients with a known or predicted difficult airway as patients with class III and IV

Modified Mallampati Score or with score > 5 wilson's risk score.

3. Patients with cardiovascular disease (congestive heart failure, coronary artery disease), history of renal or hepatic insufficiency, and endocrinal diseases were excluded from the study.

2.3 All patients were subjected to: All women were subjected to:

- The LMA size was selected according to the recommended size by the manufacturer (by weight-based formula size 3, 30-50 kg; size 4, 50-70 kg; size 5, >70 kg) (11)
- After cuff inflation with the recommended volume by the manufacturer with saline (size 3, 20 ml; size 4, 30 ml; size 5, 40 ml)) (5) the PLMA was connected to the anesthesia breathing system.
- The correct placement was judged by the ability to ventilate the patient without substantial leak at an airway pressure ≤20 cm H2O, observation of EtCO2 trace and auscultation of breath sounds.
- The position of LMA was assessed by another anesthetist (blinded assessor) using the fiberoptic laryngoscope (KARL STORZ 11301BN1, Germany) (licensed use of the table from the Springer Publishers) as devised by Aoyama et al.(4)
- Anesthesia was maintained with 1.5-2% sevoflurane in 50% oxygen-air mixture and atracurium besylate top up doses 0.1mg/kg/30 min.
- Once surgery is completed, sevoflurane was discontinued, any residual neuromuscular block was antagonized with neostigmine 0.04 mg/kg and atropine 0.02 mg/kg, then when the patient breathed spontaneously with adequate tidal volume and sufficient

efforts, and opened his or her mouth following our command, the airway device was removed after pharyngeal suctioning and lifting of the jaw. Then the patient was transferred to recovery room for observation.

- Also, assessment of pharyngolaryngeal complications (blinded assessor) was made at the time of LMA removal and again at 1 and 2 hours post-operatively.

Statistical methodology

Continuous variables were summarized as mean \pm SD and categorized variables were expressed as proportion (%). The Student t test was used to compare the groups for parametric data (age, weight, insertion time) while categorical data (gender, ASA-status, airway morbidity, fibreoptic view of the larynx) was compared using Chi square test,

Fisher exact test or Mann-Whitney U test (whichever applicable). All statistical calculations were done using computer programs Microsoft Excel 2010 (Microsoft

Corporation, NY, and USA) and SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) version 21 for Microsoft Windows. The p-value <0.05 was taken as significant. **Demographic data**

o L			
	1st group (B)	2nd group (U)	P Value
	N=51	N=51	
Age	34.45 ± 15.18	40.68 ± 17.444	0.093
Sex M/F	28/23	19/32	0.116
Weight	72.75 ± 12.85	71.62 ± 13.6	0.705
ASA Group			
ASA 1	36 (70.58%)	32 (62.74%)	0.26
ASA 2	15 (29.41%)	19 (37.25%)	

3. Results:

Data are presented as mean \pm SD; number and percentage as appropriate ASA: American Society of Anesthesiology P < 0.05 was considered statistically significant

The present study included a hundred and two patients. Patients ' age ranged from (18-75) years old with an average age of 34.45+_ 15.18(SD) in 1st group (B) and 40.68 +_ 17.444 (SD) in 2nd group (U).

These data were computed using students ttest and the P value was found to be 0.093 which is not statistically significant.

Out of the total 102 case, 55 cases were females and 47 cases were males. Of the 55 female cases,23 belonged to Group B and 32 belonged to Group U. Of the 47 male cases, 28 cases belonged to Group B and 19 cases belonged to Group U. These data were computed using Pearson's chi square test and the P value was found to be 0.116 which is not statistically significant.

The mean of weight in the group B is 72.75 kgs \pm 12.85 standard deviation and that in the group U is 71.62 kgs \pm 13.6 standard deviation. By using the independent T test p value was calculated as 0.705, which is statistically insignificant.

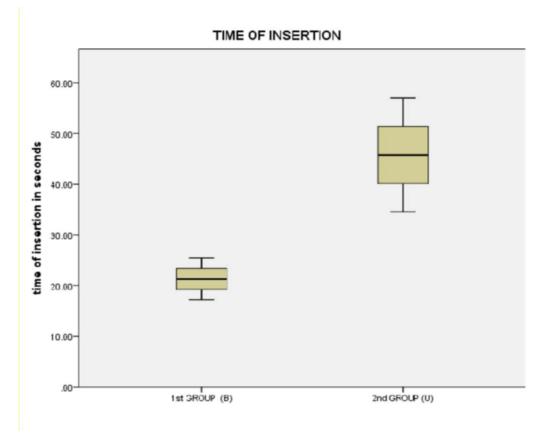
Out of the total 102 case, 68 cases were ASA1 and 34 cases were ASA2. Of the 68

ASA 1 cases,36 belonged to Group B and 32 belonged to Group U. Of the 34 ASA 2 cases, 15 cases belonged to Group B and 19 cases belonged to Group U. These data

-49- were computed using Pearson's chi square test and the P value was found to be 0.26 which is not statistically significant.

Time for insertion :

The laryngeal mask insertion time for 1st group was significantly shorter than that for the 2nd group (21.31 ± 4.116 s versus 45.7 ± 11.21 s [p < 0.0001]).

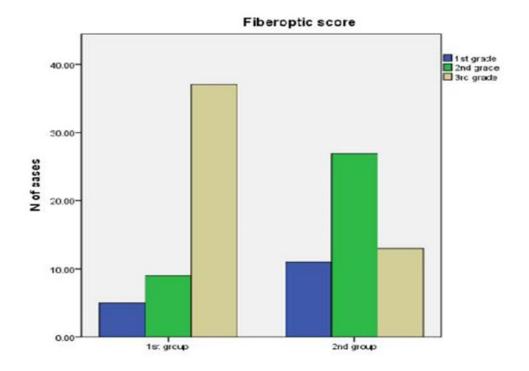


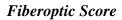
Time Of Insertion:

data were computed using students t-test and the P value was found to be <0.0001 which is highly statistically significant.

Fiberoptic score Groups:

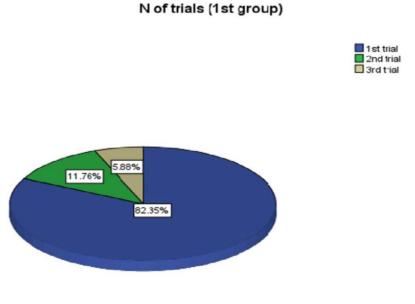
In the 1st group 9.8 % of cases showed a 1st grade of fiberoptic score, also a 17.6% of cases showed a 2nd grade of fibroptic score and 72% of cases showed a 3rd grade of fibroptic score. In the 2nd group 21.5 % of cases showed a 1st grade of fiberoptic score, also a 52.9 % of cases showed a 2nd grade of fibroptic score and 25.5 % of cases showed a 3^{rd} grade of fibroptic score. The fiberoptic glottic view scores for 2nd group was significantly better than that for the ones for 1st group (p < 0.001 by Mann-Whitney U test).





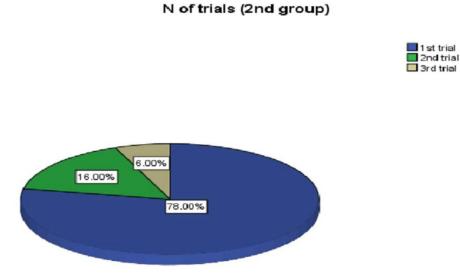
No. of trials * Groups

In 1st group (B), the LMA was successfully inserted in 42 patients (82.35%) at the first attempt, in 6 patients (11.77%) at the second attempt, and in three patients (5.88%) at the third attempt.

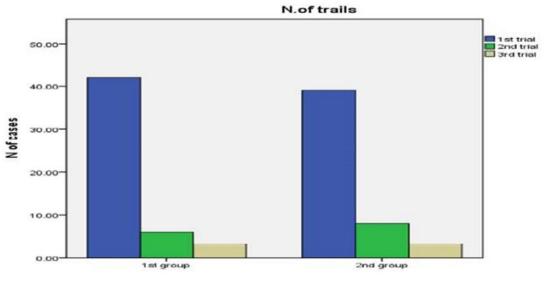


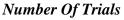
Number Of Trials In 1st Group

In the 2nd group(U), the LMA was successfully inserted in 39 patients (76.5%) at the first attempt, in 8 patient (15.7%) at the second attempt, and in 4 patients (7.8%) at the third attempt.



Number Of Trials In 2nd Group



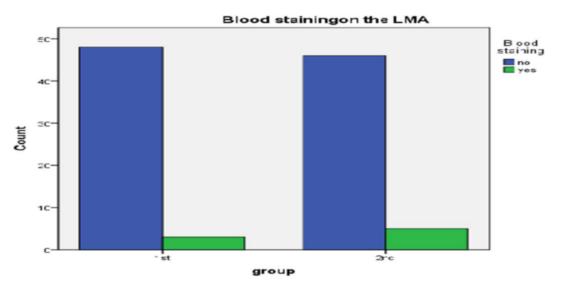


There was no statistical difference between two groups regarding to success of insertion of LMA (p = 0.476 by Mann-Whitney U test)

Complications:

Blood staining on the LMA

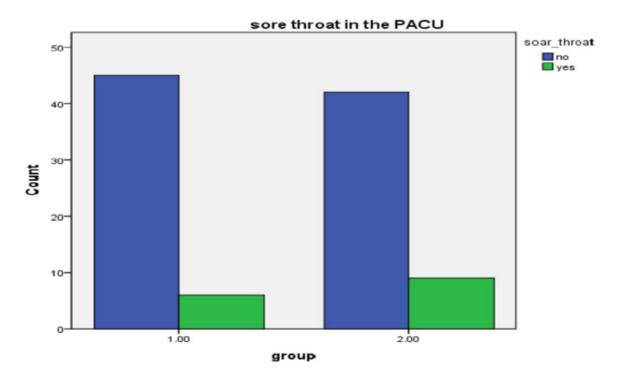
Blood staining on the LMA after removal was (3/51(5.9%)) in 1st group vs. 5/51(9.8%) in 2nd group, P = 0.715 by Fishers exact test which was statistically not different.



Blood staining on the LMA

Sore throat checked in the PACU

The incidence of sore throat checked in the PACU before discharge was 6/51 (11.8 %) vs. 9/51 (17.6 %); P = 0.557 by Fishers exact test which was statistically insignificant.



Sore throat checked in the PACU

4. Discussion:

This randomized study was designed to compare between the blind technique and US guided technique of laryngeal mask airway insertion regarding the position as confirmed by the fiberoptic laryngoscope.

In adults, the Successful insertion of LMA assessed clinically by effective

ventilation, and the airway pressure generated from ventilation, showed a good correlation with correct LMA positioning. (15) However, several studies have shown that blind insertion of LMA often results in suboptimal positioning. These studies (involving lateral neck radiography, computed tomography, and magnetic resonance

imaging) have shown that the epiglottis is deflected posteriorly in >80% of patients after blind insertion of Supra glottic airway devices, (16) Fibreoptic viewing also reveals that the epiglottis is deflected to suboptimal positions in 50–80% of insertions, and the epiglottis tip can be seen within the bowl of the LMA. (17).

Positioning can be confirmed by fibreoptic evaluation, on which vocal cords were clearly seen, often with the posterior part of epiglottis visible (but not the tip) and with the cuff optimally placed on the midline. Fibreoptic scoring was used in previous studies; however, different results were reported. Campbell et al. found that 91.5% of direct laryngoscopy patients had an ideal LMA insertion position; however, an ideal fibreoptic position was observed in 42% of patients in the standard digital group. (12). Videolaryngoscopy provides visualization of the epiglottis and can prevent downfolding of the epiglottis, distal cuff misplacement and backward folding, as well as proximal LMA cuff displacement during LMA placement. Therefore, video laryngoscopy may improve insertion conditions and prevent airway gas leaks, airway obstruction and impaired gas exchange. (18).

Zhou Z et al compared LMA placement with US, fiberoptic laryngoscope and clinical tests; of the 64 women, placement was confirmed as acceptable in 89.1% by clinical tests, in 59.4% bv fiberoptic laryngoscope assessment and in 67.2% by ultrasound examination. With respect to patients with oropharyngeal leaks classified as high, there were no differences in confirmation of acceptable placement between clinical tests and ultrasound examinations (p = 0.092), but the number of patients determined to have acceptable placement by ultrasound examination was greater than that determined by fiberoptic laryngoscopy (p = 0.034). According to the results of this study, it can be concluded that examination ultrasound is a superior technique for confirming the seal on the LMA. (19)

S. N. Chandan et al compared between blind insertion of LMA and laryngoscope guided

insertion. There was no statistically significant difference between both groups (P=0.279) in terms of Campbell category. There was no statistically significant relation between Wilson airway score or Mallampati class and Campbell category (p=0.633 and 0.239 respectively). According to the results of this study, the authors concluded that blind insertion technique is easier and simpler method for insertion of LMA and has a -55reasonable success during insertion, so it is recommended to be used. (20).

Weryana M et al compared between blind insertion of LMA and laryngoscope guided insertion. The incidence of correct insertion of the LMA by videolaryngoscope was significantly higher than the use of the classic blind insertion technique based on FLS assessment (79.2% vs 17%, p < 0.05) and clinical score (100% vs 88.7%, p < 0.05).

The first attempt success insertion rate of LMAs was superior in the group using videolaryngoscopy (100% vs 88.7%, p < 0.05). The incidence of sore throat was not statistically significantly different between the two groups, while for blood staining present on the LMA cuffs upon removal, a significantly higher incidence was observed with the blind technique with p value 0.028. According to the results of this study, it can be concluded that video laryngoscope is a useful tool for insertion and guiding the LMA in a correct position. The camera on the tip of the video laryngoscope blade provides a wider

angle view than that obtained with classic laryngoscopes, and thus we can place LMA in front of the vocal cords more easily. (21)

Ultrasonography has been used to confirm the position of the LMA cuff. Proper cuff position to seal the larynx is required for adequate ventilation through the LMA.

The LMA cuff was inflated with fluid and the position of the LMA cuff was seen by US from the lateral approach. If the LMA was not visualised by US equally on both sides of the larynx, it can be subsequently repositioned correctly. (14)

Ultrasound examination is a fast, noninvasive and reliable means of detecting

LMA misplacement that agrees closely with the leakage test. (13)

Song K et al confirmed the position of LMA using ultrasound. Seven patients

(12.1%) required LMA reinsertion, and ventilation was inadequate in a further 6 patients (10.3%). Three patients (5.2%) developed laryngospasm and inspiratory stridor after insertion resulting in inadequate ventilation, but none needed reinsertion as optimal placement was confirmed by fiberscope. (22)

JM Kim et al designed a study to estimate the incidence of LMA malposition detected with US in pediatric patients. The incidence of LMA malposition was higher with FOB (P < 0.0001), but the incidence of rotation was similar (P = 0.395). US

arytenoid grade did not correlate with FOB LMA grade (P = 0.611) but showed a significant correlation with LMA rotation grade (P < 0.0001; 95% CI, 60%–83%). They concluded that US could not detect the suboptimal depth of the LMA, but has the promise of being an accurate tool for detecting a rotated LMA. (23)

Gupta et al. reported that the US grade of LMA position closely correlated with the FOB LMA grade in adult patients. Although they graded LMA positioning as a degree of structural indentation by the LMA cuff relative to the pre procedural image on an airway manikin, they did not present any US image changes after LMA placement (13)

-56- In our study, the laryngeal mask insertion time for 1st group (blind technique) was

significantly shorter than that for the 2nd group (US guided technique).

Kim GW et al. found that the time taken for insertion of the LMA was significantly longer in the laryngoscope-guided insertion group, compared to blind insertion group $(35.9\pm9.5s$ vs. 28.7±9.5s, p<0.0001 (24).also the insertion time was longer (by approximately 10 s) in the videolaryngoscope-guided insertion group than in the standard digital insertion group (38 vs 28s)(25). Our results are also similar to these findings. However, the difference is not clinically important, as emphasized in previous studies. (26)

In this study, the first attempt success rate for insertion of the LMA was not

significantly different between the two groups, where the LMA was successfully inserted in 42 patients (82.35%) in 1st group (B), and was successfully inserted in 39 patients (76.5%) In the 2nd group (U). Our 82.35% success rate in the first attempt for the standard technique was similar to that observed in previous studies which reported success rates of 67–93% for the first attempt at inserting LMA with blind technique.(27)

The reported incidence of Postoperative sore throat after general anesthesia with the use of the supraglottic airways is up to 35%, (28)

The overall incidence of sore throat in our patients was 14.7% (15/102) which was relatively low compared with previous reports and there was no significant difference between the two groups where the incidence of sore throat checked in the PACU before discharge was 6/51(11.8%) for the blind technique vs. 9/51(17.6%) for the U/S guided technique

The presence of blood on the device upon removal of the LMA often indicates minor trauma associated with device insertion. In our study it was 5.9% (3/51) in 1st group vs. 9.8% (5/51) in 2nd group with P = 0.715 which was statistically not different.

The overall incidence of Blood staining on the LMA after removal in our patients was 7.8% (8/102) which was reasonably similar to Nakayama finding. (29)

The reported incidence of this for the cLMA is between 12 and 15% (30) and 9 and 22% in association with the PLMA, (31) depending on insertion technique.

Limitations of the study:

The use of ultrasound and fiberoptic bronchoscopy is dependent on operator competencies and requires schooling and has a steep gaining knowledge of curve.

A high degree of bodily agility and knowledge of appropriate sonoanatomy is required to turn out to be proficient in its use. (32)

5. Conclusion:

U/S has many advantages for imaging the airway, it is safe, non-invasive, quick, portable, widely available, and gives real-time dynamic images of the airway.

Ultrasound examination can further give insight into the cause of airway/ventilation events that may be interfering with the LMA placement and ventilation.

Ultrasound examination can replace fiberoptic examination for confirmation of the correct placement of an LMA. U/S can assist in appropriate repositioning of the LMA helping for optimal LMA positioning.

6. References:

- 1. Agarwal A, Shobhana N. LMA in neurosurgery. Can J Anesth. 1995;42:750.
- Anatomy of the larynx, trachea and bronchi. Anaesthesia and İntensive Care Medicine. 2011;12:8.

- 3. Anonymous fiberoptic infections. Lancet 1980;ii:782-3.
- Aoyama K, Takenaka I, Sata T, Shigematsu A: The triple airway manoeuvre for insertion of the laryngeal mask airway in paralyzed patients. Can J Anaesth; 1995;42:1010-6.
- Arul DA, R. Jacob MD, DA. A different under vision approach to a difficult intubation. Paediatric Anaesthesia 1999; 9(3) 260.
- Asai T, Morris S. The laryngeal mask airway: its features, effects and role. Can J Anaesth. 1994;41:930–960.
- Ayappa I, Rapoport DM. The upper airway in sleep: Physiology of the pharynx. Sleep Medicine Reviews. 2003;7(1):9-33.
- Ball AJ. Laryngeal mask misplacement—a non problem. Anesth Analg. 1995;81:204.
- 9. Ball AJ. Laryngeal mask misplacement—a non problem. Anesth Analg. 1995;81:204.
- Bannister HL. Respiratory system.
 Gray's anatomy. 38th edition. ELBS Churchill Livingstone 1995.
- Bennett J, Petito A, Zandsberg S. Use of the laryngeal mask airway in oral and maxillofacial surgery. J Oral Maxillofac Surg. 1996;54:1346–1351.
- Campbell RL, Biddle C, Assudmi N, Hotchkiss M: Fiberoptic assessment of laryngeal mask airway placement: blind insertion versus direct visual epiglottoscopy. J Oral Maxillofac Surg; 2004, 62:1108-13. -64-

- Gupta D, Srirajakalidindi A, Habli N, Haber H. Ultrasound confirmation of laryngeal mask airway placement correlates with fiberoptic laryngoscope findings. Middle East J Anaesthesiol 2011; 21: 283-287.
- Hatfield A, Bodenham A. Portable ultrasonic scanning of the anterior neck before percutaneous dilatational tracheostomy. Anaesthesia 1999;54:660-3.
- Joshi S, Sciacca RR, Solanki DR, Young WL, Mathru MM. A prospective evaluation of clinical tests for placement of laryngeal mask airways. Anesthesiology 1998;89:1141–6.
- 16. Shorten GD, Opie NJ, Graziotti P, Morris I, Khangure M. Assessment of upper airway anatomyin awake, sedatedand anaesthetised patients using magnetic resonance imaging. AnaesthIntensiveCare1994;22:165–9.
- 17. Moustafa MA, Abdelhady MM. Fiberoptic assessment of the laryngeal mask airway (Laryseal) position after one hour of positive pressure ventilation: an observational study. J Clin Anesth 2014;26:480–4.
- 18. van Zundert AAJ, Wyssusek KH, Pelecanos A, Roets M, Kumar CM. A prospective randomized comparison of airway seal using the novel vision-guided insertion of LMA-Supreme® and LMA-Protector®. J Clin Monit Comput. 2019;

https://doi.org/10.1007/s10877-019-

<u>00301-3</u>. [Epub ahead of print].)

- 19. Zhou Z F, Chen- Zhong xia, Meng Wu, Li
 Na Yu, Guo- Zhang Yan, Qiu-Sheng Ren, Ci- Xian Hu, Min Yan. Comparison of three methods for the confirmation of LMA placement in female patients Undergoing Gynecologic surgery. J. Ultras med bio. 2014.12.002.
- 20. S.N.Chandan, S. M. Sharma, U. S. Raveendra and B. Rajendra Prasad. Fiberoptic assessment of laryngeal mask airway placement. a comparison of blind insertion and insertion with the use of a laryngoscope. J Maxillofac Oral Surg. 2009 Jun;8(2):95-98.
- 21. Wiryana M, AAJ Van Zundert, Sinardja K, Tjokorda Gde Agung Senapathi, I Gusti Ngurah Mahaalit Aribawa, I Gusti Putu Sukrana Sidemery and Doddy Timboel Soedarso. Accuration insertion LMA with Video Laryngoscope Compre with classic technique. SOJ Anesthesiol Pain Manag 4(1):1-4.
- 22. Song K, Yi J, Liu W, Huang S, Huang Y. Confirmation of laryngeal mask airway placement by Ultrasound examination : a pilot study. J of Clinical Anesthesia 34,2016,638-646.
- 23. JM Kim, JY Kim, WO Kim, HK kil. An ultrasound evaluation of laryngeal mask airway position in pediatric patients: an observational study. Anesthesia and Analgesia 2015;120(2):427-432.

- 24. Kim GW, Kim JY, Kim SJ, Moon YR, Park EJ, Park SY. Conditions for laryngeal mask airway placement in terms of oropharyngeal leak pressure: a comparison between blind insertion and laryngoscope-guided insertion. BMC Anesthesiol. 2019;19:4.
- 25. Ozgul et al. Comparison of videolaryngoscope-guided versus standard digital insertion techniques of the ProSealTM laryngeal mask airway. BMC Anesthesiolog (2019) 19:244. -70-
- 26. Hernandez MR, Klock PA Jr, Ovassapian A. Evolution of the extraglottic airway: a review of its history, applications, and practical tips for success. Anesth Analg. 2012;114:349–68.
- 27. Kim HC, Yoo DH, Kim HJ, Jeon YT, Hwang JW, Park HP. A prospective randomised comparison of two insertion methods for igel placement in anaesthetized paralysed patients: standard vs. rotational technique. Anaesthesia. 2014;69:729-34.) (Mc Crirrick A, Ramage DT, Pracilio JA, Hickman JA. Experience with the laryngeal mask airway in two hundred patients. Anaesth Intense Care.) 1991;19:256-60.
- 28. L'Hermite J, Dubout E, Bouvet S, et al. Sore throat following three adult

supraglottic airway devices: a randomised controlled trial. Eur J Anaesthesiol. 2017;34:417–24.

- 29. Nakayama S, Osaka Y, Yamashita M. The rotational technique with a partially inflated laryngeal mask airway improves the ease of insertion in children. Paediatr Anaesth. 2002;12:416-9.
- Parker M. R. J., Day C. J. E. Visible and occult blood contamination of laryngeal mask airways and tracheal tubes used in adult anaesthesia. Anaesthesia. 2000;55(4):388–390. doi: 10.1046/j.1365-2044.2000.01281.x.
- 31. Pajiyar A. K., Wen Z., Wang H., Ma L., Miao L., Wang G. Comparisons of clinical performance of guardian laryngeal mask with laryngeal mask airway ProSeal. BMC Anesthesiology. 2015;15(1, article 69) doi: 10.1186/s12871-015-0039-3.
- 32. Maltby RJ, Beriault MT, Watson NC, et al. The LMA-ProSealTM is an effective alternative to tracheal intubation for laparoscopic cholecystectomy. Can J Anesth. 2002;49:857–862.