Laryngopharyngeal mucosal injury after prolonged use of the ProSeal™ LMA in a porcine model: a pilot study

[Lésion de la muqueuse laryngo-pharyngée suite à une utilisation prolongée du masque laryngé ProSeal™ dans un modèle porcin : une étude pilote]

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Purpose: Little is known about the potential for the cuff of the ProSeal™ laryngeal mask airway (PLMA) to cause laryngopharyngeal mucosal injury. The aim of this study was to investigate the effects of prolonged exposure of the laryngopharyngeal mucosa to the PLMA in an animal model.

Methods: The PLMA was used for positive pressure ventilation in eight German country pigs randomized to receive different durations of anesthesia lasting three to 24 hr. Two additional pigs served as controls. Biopsies from 14 predetermined areas of the laryngopharyngeal mucosa were examined histopathologically using light microscopy. The number of areas with signs of mucosal damage was evaluated, and the degree of tissue damage was analyzed using a semiquantitative scoring system.

Results: The number of areas with moderate to severe mucosal damage was 0–2 in animals anesthetized for less than 12 hr, 6 in animals anesthetized for 12–18 hr, and 12 in animals anesthetized for more than 18 hr. The severity of mucosal damage was also time-dependent, indicated by raising semiquantitative scores for epithelial and subepithelial mucosal damage.

Conclusion: The histopathological findings of this study show that prolonged use of the PLMA in the pig for up to nine hours is associated with no, or only mild alterations in the laryngopharyngeal mucosa, whereas use for 12 hr or more is associated with clear signs of mucosal injury.

Objectif : Nous ne possédons que peu de données concernant le potentiel du ballonnet du masque laryngé ProSeal™ (PLMA) de provoquer des lésions de la muqueuse laryngo-pharyngée. Le but de cette étude était d'examiner les effets d'une exposition prolongée de la muqueuse laryngo-pharyngée au PLMA dans un modèle animal.

Méthode : Le PLMA a été utilisé pour la ventilation à pression positive chez huit cochons de campagne allemands randomisés à recevoir différentes durées d'anesthésie, comprises entre trois et 24 heures. Deux cochons supplémentaires ont servi de contrôles. L'examen histopathologique des biopsies de quatorze surfaces prédéterminées de la muqueuse laryngo-pharyngée a été réalisé en microscopie optique. Le nombre de surfaces présentant des signes de lésions muqueuses a été évalué, et le degré de lésion tissulaire a été analysé à l'aide d'un système de scores semi-quantitatifs.

Résultats : Le nombre de surfaces présentant des lésions de la muqueuse modérées à sévères étaient de 0-2 chez les animaux anesthésiés durant moins de 12 h, 6 chez les animaux anesthésiés durant 12-18 h, et 12 chez les animaux anesthésiés durant plus de 18 h. La sévérité des lésions de la muqueuse a également été associée à la durée, comme cela a été indiqué en élevant les scores semi-quantitatifs pour les lésions de la muqueuse épithéliale et sous-épithéliale.

Conclusion : Les résultats histopathologiques de cette étude montrent qu'une utilisation prolongée du PLMA chez le cochon jusqu'à neuf heures n'est associée à aucune, ou à de très faibles altérations de la muqueuse laryngo-pharyngée, alors qu'une utilisation de 12 h ou davantage est associée à des symptômes évidents de lésion de la muqueuse.

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ALTHOUGH most studies evaluating use of the laryngeal mask airway (LMA) have been undertaken in surgical procedures lasting two to three hours, several reports demonstrate the efficacy of the LMA for prolonged surgical procedures,^{1,2} or even for postoperative respiratory support.³⁻⁵ Currently, most anesthesiologists tend to limit use of the LMA-Classic® (CLMA) to short surgical procedures lasting less than three hours,^{1,6} despite the lack of scientific evidence that prolonged LMA use is generally harmful to the patient. With the advent of the LMA-ProSeal® (PLMA) in 2000,⁷ the indications of LMA use have expanded further.⁸⁻¹⁰ Recently, different authors have reported prolonged use of the PLMA for postoperative respiratory support.^{11,12} In fact, the PLMA could be used routinely for prolonged surgical procedures or postoperative respiratory support. However, this might incur problems that have not yet been observed during short surgical procedures.

There is evidence that the cuff of both the CLMA and the PLMA can exert a magnitude of pressure onto the laryngopharyngeal mucosa sufficiently high to cause lingual, hypoglossal or recurrent laryngeal nerve injury,^{13,14} or impede venous and lymphatic drainage.¹⁵ In theory, the cuff of the PLMA could impede pharyngeal mucosal blood flow to a degree that can cause laryngopharyngeal mucosal injury when the PLMA is used over a prolonged period. Therefore, before generally advocating its use for prolonged sur-

gery in patients under general anesthesia, the potential advantages and disadvantages of routine prolonged use should be investigated in a controlled fashion. As little is known about the consequences of prolonged PLMA use, basic knowledge gained in an animal study should help in the design of clinical studies in humans and make such studies safer. Histopathological studies of the laryngopharyngeal mucosa after use of the PLMA for a prolonged period have not been published. The pig is used as an experimental model for research into airway mucosal injury because of the anatomic similarity of porcine and human airways.¹⁶ Recently, it was shown that the PLMA can be used to ensure sufficient positive pressure ventilation (PPV) in the pig over a prolonged period.¹⁷ The aim of this randomized study was to investigate the effects of prolonged PLMA use on the laryngopharyngeal mucosa in pigs. Different durations of anesthesia were used to establish a time limit for prolonged use up to which point there was no apparent histopathological mucosal damage.

Methods

After approval by the State Committee on Animal Welfare, ten German country pigs (six male, four female) weighing 48 (41–55) kg were studied. Before starting the study, eight pigs were randomly allocated to different durations of anesthesia lasting three to 24 hr (Table), using the PLMA with the cuff pressure ($P_{\text{intracuff}}$) limited to 60 cm H₂O. Two animals served as control. They were anesthetized for a duration of six hours. In one pig, the airway was secured using an endotracheal tube (ETT) with the $P_{\text{intracuff}}$ limited to 20 cm H₂O (*control ETT*). In the other pig, the PLMA was used and the $P_{\text{intracuff}}$ was kept constant at 200 cm H₂O throughout the entire anesthetic (*control PLMA high $P_{\text{intracuff}}$*). Information on the allocated duration of anesthesia and airway device was contained in sealed envelopes numbered from 1 to 10 that were opened before induction of anesthesia by a study nurse not participating in the investigation. Based on the findings of a previous study, a size 4 PLMA was used in animals weighing less than 45 kg and a size 5 PLMA was used in animals weighing more than 45 kg.¹⁷

The conduct of anesthesia was identical for all animals. Food, but not water, was withheld the night before anesthesia. Preanesthetic medication in all animals consisted of azaperone 4 mg·kg⁻¹ *im*, midazolam 0.2 mg·kg⁻¹ *im*, s(+)-ketamine 2 mg·kg⁻¹ *im* and atropine 0.02 mg·kg⁻¹ *im*. After loss of consciousness, a pulse oximeter (Ohmeda, Louisville, CO, USA) was taped to the tail, a 20G intravenous cannula was placed in a dorsal ear vein, and a Hestarch 10% (200/0.5) infusion was started. While the animal

TABLE Type of airway and duration of anesthesia

Experiment	Type of airway ($P_{\text{intracuff}}$)	Duration of anesthesia (hours)
1	PLMA (60 cm H ₂ O)	6
2	PLMA (60 cm H ₂ O)	24
3	PLMA (60 cm H ₂ O)	3
4	PLMA (60 cm H ₂ O)	9
5	PLMA (60 cm H ₂ O)	15
6	PLMA (60 cm H ₂ O)	21
7	PLMA (60 cm H ₂ O)	18
8	PLMA (60 cm H ₂ O)	12
9	ETT (20 cm H ₂ O)	6
10	PLMA (200 cm H ₂ O)	6

PLMA = ProSeal™ laryngeal mask airway; ETT = endotracheal tube.

was breathing spontaneously, it was placed on an operating table in the prone position, preoxygenated ($6\text{--}8\text{ L}\cdot\text{min}^{-1}\text{ O}_2\text{ 100\%}$), and attached to an electrocardiographic monitor. Anesthesia was induced with propofol $2\text{--}3\text{ mg kg}^{-1}$ *iv*, no neuromuscular blocking drugs were administered. In nine animals, the PLMA was placed under direct laryngoscopy onto the larynx once spontaneous ventilation had ceased. In eight, the cuff was inflated to a maximum $P_{\text{intracuff}}$ of $60\text{ cm H}_2\text{O}$ (VBM Cuff Pressure Gauge, VBM Medizintechnik, Sulz, Germany), and in one animal to a maximum of $200\text{ cm H}_2\text{O}$ (*control PLMA high $P_{\text{intracuff}}$*). The initial $P_{\text{intracuff}}$ was kept constant throughout the entire duration of anesthesia. After confirmation of manual ventilation by the appearance of a CO_2 wave on the capnograph of the anesthesia machine (Sulla 808V, Draeger, Luebeck, Germany), a 14G gastric tube (G-tube) was passed through the drainage tube (DT) of the PLMA into the stomach. In one animal, endotracheal intubation was facilitated by direct laryngoscopy (*control "ETT"*). After the airway device had been taped to the maxilla, volume controlled PPV (tidal volume: $10\text{ mL}\cdot\text{kg}^{-1}$ body weight) with positive end expiratory pressure (PEEP) = $5\text{ cm H}_2\text{O}$ was started using a $F_{\text{I O}_2} = 0.5$ (oxygen in air mixture). In all animals, the respiratory rate was set to achieve an end tidal CO_2 (PetCO_2) of $35 \pm 5\text{ mmHg}$. Anesthesia was maintained with propofol $0.15\text{--}0.2\text{ mg}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$, and hourly boluses of *s(+)-ketamine* $1\text{--}2\text{ mg}\cdot\text{kg}^{-1}$. Fluid maintenance was with Ringer's lactate solution $3\text{--}5\text{ mL}\cdot\text{kg}^{-1}\cdot\text{hr}^{-1}$. A 20G arterial catheter was placed into the superficial femoral artery to facilitate continuous invasive blood pressure monitoring (Servomed Monitor, Hellige, Freiburg, Germany) and periodic arterial blood gas measurement. A 14G cannula was placed percutaneously into the urinary bladder to facilitate continuous suprapubic urine drainage. All animals were covered with blankets during the investigation in order to minimize heat loss. At the end of the study, the animals were killed by intravenous injection of 50 mmol potassium chloride.

Heart rate, invasive blood pressure, peripheral oxygen saturation (SpO_2), body temperature, PetCO_2 , tidal volume, minute volume, respiratory rate, airway pressures and $P_{\text{intracuff}}$ were monitored continuously throughout the study. A fiberoptic examination (3.5 mm flexible endoscope Karl Storz, Tuttlingen, Germany) was performed immediately after placement of the PLMA and the ETT, to verify the correct position of the airway device (i.e., with the cuff of the PLMA over the laryngeal inlet and the DT with access to the upper esophagus, or the distal end of the ETT in the trachea). In all cases in which the PLMA was

FIGURE 1 Mucosal damage - number of affected areas with signs of moderate or severe damage.

FIGURE 2 Mucosal damage - epithelial and subepithelial scores.

used, the airway leak pressure (P_{leak}) at $P_{\text{intracuff}} = 60\text{ cm H}_2\text{O}$ was determined with a fresh gas flow of $3\text{ L}\cdot\text{min}^{-1}$ after setting the ventilator to spontaneous ventilation and closing off the expiratory valve¹⁷ to verify that the seal provided by the PLMA was sufficient to allow for PPV with a tidal volume of $10\text{ mL}\cdot\text{kg}^{-1}$ body weight and PEEP = $5\text{ cm H}_2\text{O}$. Arterial blood gas analysis under a $F_{\text{I O}_2} = 1.0$ was performed after 60 min and thereafter at two-hourly intervals. At the end of the anesthetic, a second fiberoptic examination was performed and the larynx and trachea were inspected for signs of aspiration.

The pharynx and larynx of the animal were completely excised immediately after completion of the study period and fixed in 4% formalin for at least 72 hr. Biopsies from 12 predetermined areas (six on each side) in contact with the cuff of the PLMA were obtained. The locations of the areas were as follows: area 1) 1 cm below the base of the tongue, anterior wall; area 2) mesopharynx, lateral wall; area 3) mesopharynx, dorsal wall; area 4) mesopharynx, dorsal wall just above larynx; area 5) hypopharynx, dorsal wall posterior to the larynx; area 6) pyriform fossa. In addition, one biopsy was obtained from each vocal cord. The specimens were embedded in paraffin, and cut and stained with hematoxylin and eosin. All specimens underwent a standardized histopathological examination by light microscopy. The examinations were

FIGURE 3 Endotracheal tube ($P_{\text{intracuff}} = 60 \text{ cm H}_2\text{O}$), six hours: normal mucosa (hematoxylin and eosin; magnification 200x).

carried out by the same pathologist unaware of the duration of anesthesia, the airway used, or the $P_{\text{intracuff}}$. The epithelial surface was examined for signs of a) epithelial desquamation, b) erosion, and c) ulceration. The subepithelial layer was examined for signs of d) congestion, e) hemorrhage, and f) inflammatory infiltration. The degree of tissue damage was described using a semiquantitative scoring system similar to one described previously^{18,19} with scoring from 0 to 3 (0 = without damage, 1 = mild damage evident, 2 = moderate damage evident, 3 = severe damage evident). For each animal, the scores for epithelial surface damage and subepithelial tissue damage of all 12 specimens in contact with the cuff of the PLMA were totalled, and these two scores formed the total tissue damage score. The numbers of areas with moderate or severe damage (grade 2 or 3) were summated to provide a quantitative subscore of affected areas.

Data were analyzed using SPSS (SPSS Inc., Chicago, IL, USA) software. Unless otherwise stated data are expressed as mean values $\pm$ SD with (95% confidence intervals) or as mean values and (range). Descriptive analysis was used for all animals.

Results

The airway was secured in all animals at the first attempt atraumatically, and G-tube placement was successful for each experiment. No animal was excluded from data analysis. Fibreoptic inspection confirmed correct position of the PLMA and the ETT in all cases. No signs of aspiration were found by fibreoptic examination of the larynx and trachea at the end

FIGURE 4 ProSeal™ laryngeal mask airway ($P_{\text{intracuff}} = 200 \text{ cm H}_2\text{O}$), six hours: arrows indicating (from left to right) ulceration and congestion (hematoxylin and eosin; magnification 200x).

FIGURE 5 ProSeal™ laryngeal mask airway ($P_{\text{intracuff}} = 60 \text{ cm H}_2\text{O}$), six hours: normal mucosa (hematoxylin and eosin; magnification 200x).

of anesthesia in any pig. All animals were hemodynamically stable; oxygenation and ventilation were adequate throughout the entire anesthetic. Neither the ETT nor any of the PLMAs were contaminated with blood upon removal.

All specimens were adequate for histopathological examination and no gross macroscopic injury was evident on inspection. The vocal cords biopsies showed no signs of injury in any animal. The degree of injury to the laryngopharyngeal mucosa in contact with the PLMA cuff varied amongst the nine animals managed

FIGURE 6 ProSeal™ laryngeal mask airway ($P_{\text{intracuff}} = 60$ cm H_2O), 21 hr: left arrow indicating erosion, right arrows inflammatory infiltration, subepithelial edema (hematoxylin and eosin; magnification 200x).

FIGURE 7 ProSeal™ laryngeal mask airway ($P_{\text{intracuff}} = 60$ cm H_2O), 12 hr: arrows indicating (from left to right) perivascular inflammatory infiltration, congestion, and early-stage pressure necrosis (hematoxylin and eosin; magnification 200x).

with the PLMA. The number of areas with moderate to severe (grade 2 or 3) microscopic mucosal injury is displayed in Figure 1. The total score of epithelial and subepithelial mucosal damage is displayed in Figure 2.

No signs of microscopic injury were observed in any biopsy from the animal managed with an ETT (*control ETT*) (Figure 3). Clear signs of mucosal injury were evident in all 12 predetermined areas in the animal managed with the PLMA and a constant

$P_{\text{intracuff}} = 200$ cm H_2O for six hours (*control PLMA high $P_{\text{intracuff}}$*) (Figure 4).

In the animals managed with the PLMA and a constant $P_{\text{intracuff}} = 60$ cm H_2O for three to 24 hr there was a clear distinction with respect to the number of affected areas and the degree of mucosal damage between animals anesthetized for up to nine hours, 12–18 hr, and more than 18 hr (Figures 1 and 2). The number of affected areas with moderate to severe mucosal damage was 0–2 in animals anesthetized for up to nine hours, 6 in animals anesthetized for 12–18 hr, and 12 (i.e., all areas) in animals anesthetized for more than 18 hr. This was also reflected in the severity of the mucosal damage with total scores for epithelial and subepithelial damage with a maximum of 6, 21–34, and 61–66 respectively. Examples of microscopic examinations of corresponding areas (area 4: hypopharynx, above larynx) of different animals are shown in Figures 5 to 7.

Figure 5 (PLMA, $P_{\text{intracuff}} = 60$ H_2O , six hours) shows a normal stratified squamous epithelium and subepithelial layer with no sign of injury, similar to the image of Figure 3 (*control ETT*), whereas Figure 6 (PLMA, $P_{\text{intracuff}} = 60$ H_2O , 21 hr) shows clear signs of epithelial desquamation, erosion, and congestion with inflammatory infiltration, resembling the image in Figure 4 (*control PLMA high $P_{\text{intracuff}}$*). Figure 7 (PLMA, $P_{\text{intracuff}} = 60$ H_2O , 12 hr) shows an intermediate picture of injury characterized by early-stage pressure necrosis, epithelial desquamation, congestion, and perivascular neutrophilic infiltration.

Discussion

The histopathological findings of our study show that in the pig, prolonged use of the PLMA for a duration of up to nine hours is associated with no or only mild alterations in the laryngopharyngeal mucosa, whereas use of the PLMA for 12 or more hours is associated with clear signs of mucosal injury at multiple sites. These findings will assist in designing future investigations into prolonged use of the PLMA.

No previous histopathological studies examining the effects of the LMA cuff on the laryngopharyngeal mucosa during prolonged use (> three hours) have been published. This is probably because reports of laryngopharyngeal injury associated with the LMA are rare, and routine clinical use of this supraglottic airway has generally been limited to short surgical procedures lasting less than three hours.^{1,6} However, following the clinical introduction of the PLMA, the indications for use of supraglottic airways have expanded,^{8–10} and even postoperative ventilation in the intensive care unit has been suggested for selected patients.¹⁰ The

underlying rationale is that the PLMA forms a more effective seal than the CLMA and – if correctly positioned – can provide protection against aspiration.¹⁰ A major concern with prolonged use of cuffed airway devices, however, is potential mucosal damage. As with tracheal mucosal injury associated with the use of cuffed endotracheal tubes, the severity of laryngopharyngeal mucosal injury associated with the use of the LMA is probably influenced by the duration of exposure and the pressure exerted by the cuff on the mucosa.²¹ Studies investigating the role of the pressure in the severity of laryngopharyngeal mucosal injury have been conducted. Recommendations to limit cuff inflation pressure to 60 cm H₂O²² do have an evidence base, although a limitation of these studies was the use of a surrogate parameter (*pharyngeal discomfort*) for mucosal tissue damage as the primary outcome variable.^{23,24} Controlled clinical investigations to establish a time limit for safe LMA use have never been undertaken. Considering a potential expansion of the use of the PLMA for procedures lasting more than three hours or even into the postoperative period, it appears mandatory to determine a time limit beyond which use of the PLMA is not advisable because of mucosal tissue damage. Conducting such studies in humans would obviously be unethical, and an initial evidence base would have to be established in animals. An adequately powered randomized controlled animal study comparing the use of the PLMA *vs* the ETT over different clinically relevant periods would enable investigators to plan clinical studies without an apparent risk for participating patients.

The present time-finding study provides the first relevant information to aid in the design of an appropriate, large-scale animal study. The findings indicate that use of the PLMA for 12 hr or more may be associated with laryngopharyngeal mucosal injury and suggest that there is a relationship between the degree of mucosal injury and the duration of PLMA use. The finding of no relevant tissue damage after up to nine hours of use may well be a clinically relevant finding if confirmed in a large-scale study, as only few routine surgical operations last longer than nine to ten hours. The potential limit of nine hours for “prolonged intraoperative use” would ideally be one of the endpoints, but because a considerable change in the degree of mucosal injury was found after more than 12 hr and 21 hr of use, these time limits should be included as potential endpoints of prolonged “postoperative use”.

Despite its preliminary nature, the results of this study strongly support the need to conduct further research into laryngopharyngeal mucosal injury associated with the use of the PLMA because they are in

clear contrast to findings of a clinical study by Keller and Brimacombe²⁵ who found that directly measured mucosal pressure of the CLMA and PLMA was less than capillary perfusion pressure,²⁶ and therefore concluded that mucosal ischemic injury would be uncommon with the use of either device. The results of our time-finding study suggest that their conclusion, based on single measurements, might not be applicable to prolonged PLMA use.

Our study has several limitations. First, the exploratory nature of the investigation and the small number of animals did not allow statistical evaluation of the differences between the degree of damage after different periods. Another limitation is that the study was in an animal with a different airway system from humans. However, the histological structure of the laryngopharyngeal mucosal tissue in the pig is similar to that in humans. An animal model is also the only means of investigating tissue damage by taking tissue from planned sites, instead of using surrogate parameters such as *pharyngeal discomfort*. A further criticism may be that we did not measure the mucosal tissue pressure directly as in the study by Keller and Brimacombe.²⁵ The accuracy of mucosal pressure monitoring by the use of microsensors designed for measuring cerebrospinal fluid pressure has, however, been criticized.²⁷ As we wanted to apply prolonged PLMA use under similar conditions as in routine clinical use, we ensured a constant cuff pressure of 60 cm H₂O by continuous P_{intracuff} monitoring, a clinically well accepted method of monitoring.

In conclusion, this time-finding study examining the effects of prolonged PLMA use on the laryngopharyngeal mucosa in an animal model provides histopathological evidence that prolonged use of the PLMA in the pig for up to nine hours is associated with no, or only mild alterations in the laryngopharyngeal mucosa, whereas use for 12 hr or more is associated with clear signs of mucosal injury. The observation that prolonged use of the PLMA is associated with clear signs of mucosal injury warrants further investigation. Our observations challenge the assumption that mucosal ischemic injury with the use of PLMA is uncommon because the directly measured mucosal pressure of the PLMA is lower than capillary perfusion pressure. Further large-scale animal studies are warranted before conducting clinical trials to examine the local tissue effects associated with longer-term ventilation using supraglottic airway devices.

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