

Nociceptive stimulation during Macintosh direct laryngoscopy compared with McGrath Mac videolaryngoscopy

A randomized trial using indirect evaluation using an automated administration of propofol and remifentanyl

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Abstract

Background: Decrease of the nociceptive stimulation induced by laryngoscopy could be an advantage for patients without risk of difficult intubation. The present study aimed to compare the difference in nociceptive stimulation between the use of a conventional laryngoscope or of a videolaryngoscope. Amount of nociception was assessed indirectly using the peak remifentanyl concentration determined by a closed-loop administration of propofol and remifentanyl with bispectral index (BIS) as the input signal (target 50).

Methods: A prospective single-center randomized study was performed including surgical patients without predictable risk of difficult mask ventilation or of difficult tracheal intubation. Forty consecutive surgery patients were randomly assigned to CL group (conventional laryngoscope) or VL group (McGrath Mac videolaryngoscope). Induction of anesthesia was performed automatically using the closed-loop system and myorelaxation with atracurium. The allocation was revealed just before tracheal intubation. The primary outcome was the peak plasma remifentanyl concentration observed during the 5-minute period which followed intubation.

Results: Sixteen patients in the CL group and 11 in the VL group were analyzed. Plasmatic remifentanyl and propofol concentrations were similar in both groups either before tracheal intubation or during the 5 minutes following intubation. There was a nonsignificant between-group difference ($P = .09$) for the peak concentration of remifentanyl. A comparable result was observed for other outcomes except for the heart rate which increased in the CL group.

Conclusion: Use of the videolaryngoscope McGrath Mac did not reduce the nociceptive stimulation induced during intubation as evaluated by the automatically administered remifentanyl concentration.

Trial registration: ClinicalTrials.gov, NCT02245789.

Abbreviations: BIS = bispectral index, CL = conventional laryngoscope, LMA = laryngeal mask airway, VL = videolaryngoscope, VLS = videolaryngoscopes.

Keywords: anesthesiology, closed loop, tracheal intubation

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1. Introduction

Indications for video-assisted laryngoscopy are still under debate. Hagberg and Connis^[1] recently published the Difficult Airway Society 2015 guidelines for the management of unanticipated difficult intubation in adults which states that “there is insufficient evidence to indicate that video-assisted laryngoscopy should replace direct laryngoscopy in patients with normal or difficult airways.” But in the same sentence they wrote that “as more videolaryngoscopes are introduced into clinical practice and as more practitioners become increasingly skilled with the technique of video-assisted laryngoscopy, it could well become the standard for both routine and difficult intubations.”

The videolaryngoscope is principally used to limit the risk of difficult intubation but the demonstration of decreased nociceptive stimulation and consequently of its hemodynamic consequences would represent a major point in favor of its wider use, that is, for patients without increased risk of difficult intubation. Thus, the hypothesis of this randomized study, including patients without criteria for difficult intubation, is that the use of a videolaryngoscope induces less pronounced nociceptive stimulation and, consequently, that the required maximal concentration of remifentanyl is lower than with a standard laryngoscope. To avoid any human bias, propofol and remifentanyl were

automatically administered using a closed-loop system which uses the bispectral index (BIS) as the input signal and modifies the effect site target concentrations of both drugs according to the BIS variations to maintain a target at 50.^[2] This closed-loop system has previously been used to evaluate the anesthetic effect of a conversational hypnotic session^[3] or of some drugs (nitrous oxide,^[4] dexmedetomidine),^[5] and to evaluate the analgesic effect of intraoperative use of epidural analgesia.^[6]

2. Materials and methods

This prospective, randomized, single-blinded study, performed in a tertiary hospital, was approved by the Ethics Committee (Hospital A. Paré, Boulogne Billancourt, France) and the French Regulatory Office and registered on the Clinical Trials Web Site (registration number NCT02245789).

2.1. Study population

Consecutive patients aged between 18 and 80 years, undergoing elective surgery requiring orotracheal intubation, were recruited after they gave their written informed consent. Exclusion criteria included pregnant and breast-feeding patients, predictable risk of difficult mask ventilation or of difficult tracheal intubation, necessity of a rapid sequence induction, a contra-indication to the use of the automated administration of propofol and of remifentanyl. These included known allergy to propofol or remifentanyl, psychiatric illness, supraspinal neurological disorders, cranial neurosurgical procedures, and patients equipped with a pacemaker, a contra-indication to the use of atracurium. Patients scheduled for an otolaryngological, thoracic, or intracranial surgical procedures were excluded from the study.

2.2. Anesthesia procedure

Patients' baseline characteristic data were collected before the procedure.

Patients did not receive any premedication. Upon arrival in the operating room, a dedicated peripheral intravenous cannula for the administration of IV anesthetics was placed on the forearm, and routine monitoring was performed including monitoring of neuromuscular function at the adductor pollicis. The BIS electrode (Zipprep; Bispectral Index, Covidien, Mansfield, MA) was positioned on the patient's forehead and connected to an A-2000 XP (version 3.11) BIS monitor (Covidien, Mansfield, MA).

Each patient was preoxygenated with 100% O₂ during 3 minutes or until end-tidal O₂ reached $\geq 90\%$. Thereafter, induction of anesthesia was induced automatically using the closed-loop system, the investigator choosing the initial propofol effect-site target concentration according to his/her clinical judgment. The remifentanyl effect site target concentration was determined by the controller.^[2] Atracurium, 0.5 mg/kg, was administered once the patient was unconscious to facilitate tracheal intubation, and its dosage was adjusted thereafter according to the monitoring of neuromuscular function.

Patient allocation to each group was determined after the anesthetic induction and the verification of possibility of manual ventilation. Randomization was performed using an internet connection to the Anesloop site (<https://www.anesloop.org/>) with a 1:1 scheme and balanced blocks of 10 patients: CL group (conventional Macintosh laryngoscope [Comepa, Bagnolet, France]) or VL group (McGrath Mac videolaryngoscope

[Covidien France SAS, Courbevoie, France]). The allocation was revealed just before laryngoscopy. Tracheal intubation was performed with a standard Mallinckrodt (Paris, France) oral tracheal tube (size 7 for women and 7.5 for men, except for special cases). Each time, the physician could decide to use a bougie or stylet, to apply laryngeal pressure, to change technique, to use a laryngeal mask or another ventilation device if needed (LMA Fastrach [Teleflex Medical SAS, Le Faget, France], fiberoptic bronchoscopy, trans-tracheal oxygenation, tracheotomy, or even awakening).

Maintenance of anesthesia was also performed automatically with propofol and remifentanyl. Throughout the procedure, the investigator could override the automated system if necessary or switch between closed-loop and manual control at any time.

The incidence of postoperative hoarseness or sore throat was recorded using a binary questionnaire the following day during the postoperative visit.

2.3. Outcomes

The primary outcome was the peak plasma remifentanyl concentration during the 5-minute period which followed the intubation. The concentration of remifentanyl was obtained from the Infusion Toolbox 95 software platform which calculates the effect-site concentrations of remifentanyl every 5 seconds.

The secondary outcomes concerned also anesthesia: maximal propofol site effect concentration (Toolbox 95 software platform) and BIS value observed during the 5 minutes which followed the tracheal intubation.

Other secondary outcomes concerned tracheal intubation: intubation time (time between entry of the laryngoscope into the mouth and the first capnogram), visualization of the glottis (score of Cormack and Lehane modified by Yentis,^[7] percentage of glottic opening scale),^[8] number of attempts, requirement of backward, upward, and rightward pressure of larynx, sensation of abnormal force necessary to intubate, use of alternative techniques for intubation (bougie, stylet, LMA Fastrach), hemodynamic consequences of tracheal intubation (heart rate, systolic blood pressure), occurrence of a complication during intubation (arterial oxygen desaturation [SpO₂ <92%], dental damage, oropharyngeal trauma, esophageal intubation), and postoperative sore throat and hoarseness. All these variables were noted by an observer.

2.4. Statistical analysis

Based on the analysis of a retrospective series of 50 patients having anesthetic induction performed with the dual-closed loop, we determined that the maximal target concentration of remifentanyl during the 5 minutes after intubation was 9.1 ± 2.1 ng/mL. Power analysis showed that 22 patients were required for each group in order to demonstrate a 20% reduction of the remifentanyl concentration with 80% power at the 0.05 level of significance (bilateral test). Therefore, we recruited 50 patients in total to account for possible drop-outs. Data are presented as medians (25th and 75th percentiles) or number (percentages).

As data for remifentanyl and propofol concentrations and BIS were recorded every minute, a full mixed model with interaction for repeated values was fitted with treatment group and time as factors, and preintervention value as a covariate; a compound symmetry pattern was used for variance-covariance with forced positive coefficients. For all other parameters, comparisons between groups were performed with the nonparametric

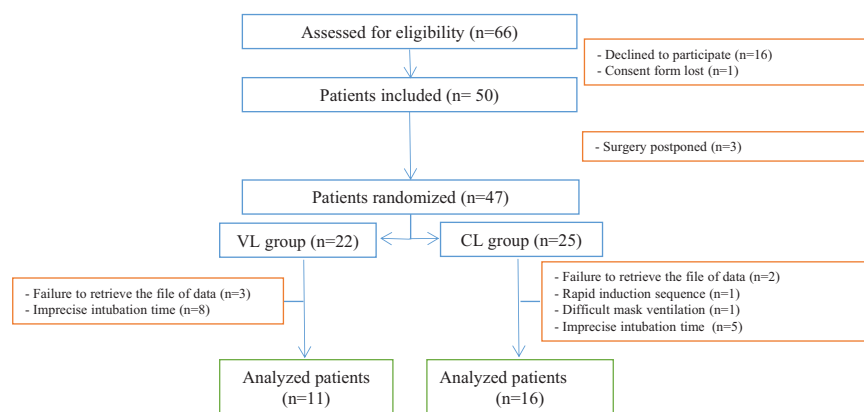


Figure 1. Study flow diagram. VL group: McGrath Mac videolaryngoscope group. CL group: Conventional Macintosh laryngoscope group.

Mann–Whitney *U* test (corrected for ties) for continuous variables and with the Fisher exact test for categorical variables. *P* < .05 was considered statistically relevant. Statistical analysis was performed with NCSS (NCSS 11 Statistical Software [2016]. NCSS, LLC. Kaysville, UT, ncss.com/software/ncss).

3. Results

Patients were recruited between September 2014 and February 2015; the Consort Flow Diagram is presented in Fig. 1. Sixty-seven patients were initially approached, finally they were 16 patients in the CL group and 11 in the VL group.

3.1. Patient characteristics

Patient characteristics and ease of manual mask ventilation are summarized in Table 1. Both groups had similar characteristics.

3.2. Anesthetic drug concentrations, BIS values, and hemodynamic variables

The closed-loop was used successfully in all cases and the investigator had never to override the automated system or to switch between closed-loop and manual control.

There was a nonsignificant between-group difference for the peak concentration of remifentanyl observed after intubation, the main outcome, when the baseline level is used as a covariable: 3.8 (2.1–7.0) ng/mL in the VL group and 5.0 (4.2–6.6) ng/mL in the CL group (*P* = .09).

Plasmatic propofol and remifentanyl concentrations automatically administered by the dual-loop system and BIS values were similar in both groups either before tracheal intubation or during the 5 minutes following intubation (*P* = .18, *P* = .19, and *P* = .16 for propofol concentrations, remifentanyl concentrations, and BIS values respectively; Fig. 2). Heart rate and systolic arterial pressure were similar in both groups before tracheal intubation. Evolution of heart rate after intubation differed between groups with an increase in the CL group while variations in systolic arterial pressure were similar (Table 2).

3.3. Characteristics of intubation

All outcomes related to tracheal intubation were similar in both groups. In the vast majority of cases, tracheal intubation was easy and without complication groups (Table 3). The duration of intubation was longer in the VL group than in the CL group but the difference did not reach statistical significance. On the contrary, external moving/pressure of the larynx was performed in 8 (50%) patients of the CL group but in only 1 patient (9%) of the VL group (*P* = .04). Postoperative hoarseness and sore throat occurred in around half of the patients whatever the group. For statistical supplementary information refer to V2 supplemental digital content, <http://links.lww.com/MD/B869>).

4. Discussion

Our study is the first aiming to compare the contribution of a videolaryngoscopes (VLS) compared with a conventional

Table 1
Patient characteristics.

	CL group n = 16	VL group n = 11	<i>P</i>
Age, y	55.5 [41.8–68.0]	58.0 [28.0–61.0]	.20
Gender, male/female	5 (31.2)/11 (68.8)	3 (27.3)/8 (72.7)	1.0
Weight, kg	69.0 [54.2–77.2]	61.0 [56.0–73.0]	.29
Height, cm	167.5 [164.0–170.0]	165.0 [159.0–174.0]	.79
ASA physical status, I/II/III	5 (31.2)/11 (68.8)/0 (0.0)	7 (63.6)/3 (27.3)/1 (9.1)	.07
Ease of manual ventilation before intubation, grade I/grade II	11 (68.8)/5 (31.2)	5 (50.0)/5 (50.0)*	1.0

Group CL: conventional Macintosh laryngoscope.

Group VL: McGrath Mac videolaryngoscope.

Results are presented as medians [25th and 75th percentiles] or number (percentages).

P values obtained through randomization test (Monte–Carlo with 10,000 iterations) for continuous variables and through Fisher exact test for categorical variables.

* 1 missing value.

ASA, American Society of Anesthesiologists.

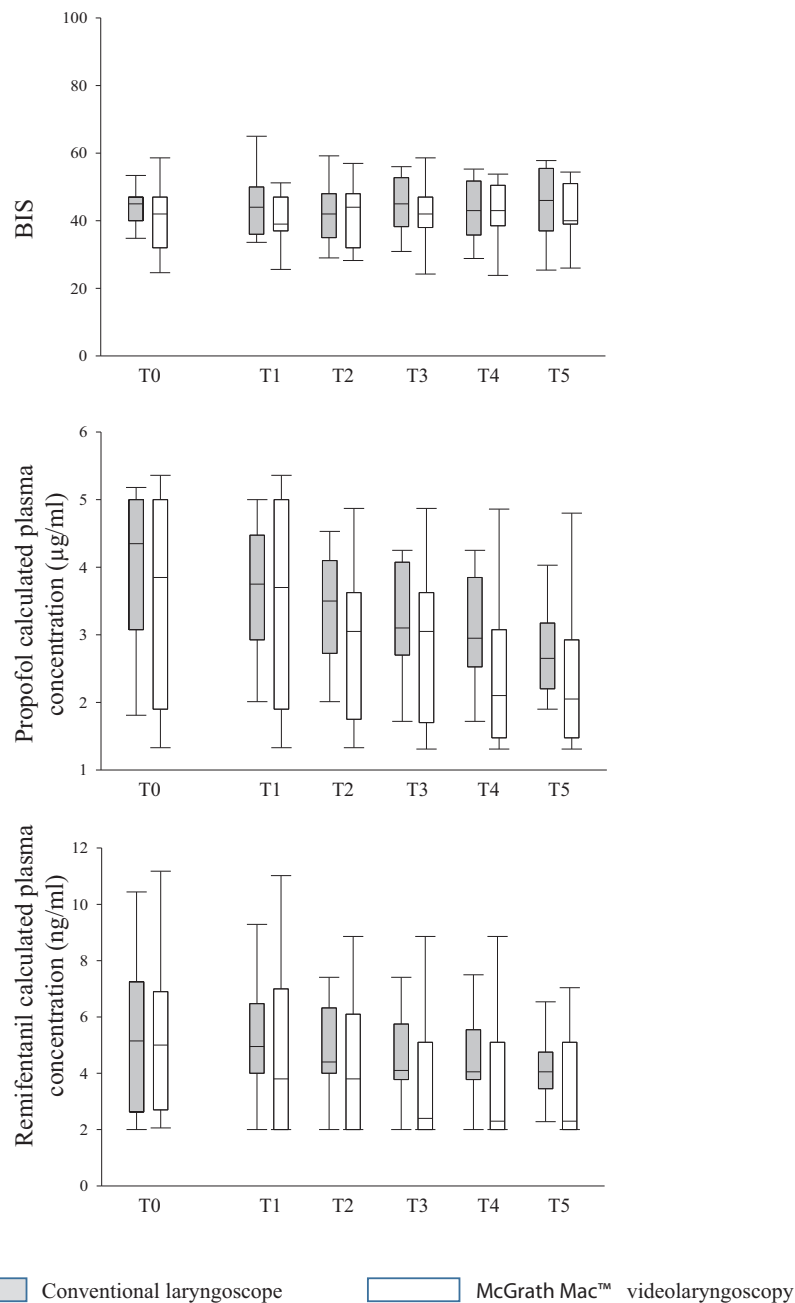


Figure 2. BIS values (up), propofol calculated plasma concentrations (middle), remifentanyl calculated plasma concentrations (bottom) before (T0) and during the 5 minutes after intubation (T1–T5). Calculated used the pharmacokinetic models of Schnider for propofol^[9] and Minto for remifentanyl.^[10] Representation uses box plots (median, 25 and 75 percentiles, 10 and 90 percentiles). BIS=Bispectral index. T1 to T5: first to fifth minutes after intubation. Grey boxes: conventional laryngoscope. White boxes: McGrath Mac videolaryngoscopy.

laryngoscope in terms of nociception in patients without risk factors for difficult intubation using a dual-loop system. This randomized study showed similar plasma peak remifentanyl and propofol concentrations after the intubation. All other recorded variables, except heart rate, were also similar. All variables concerning intubation and its modalities were also similar apart from its duration which was significantly longer when the videolaryngoscope McGrath Mac was used even though the blades of both laryngoscopes had the same shape.

Monitoring of nociception in the patient under general anesthesia relies on the study of physiological responses caused by a noxious stimulus. Several systems based on the vascular

sympathetic response (skin conductance), cardiac and vascular sympathetic response (surgical pleth index), parasympathetic cardiac response (analgesia nociception index), and on the assessment of the pupillary reflex dilatation are emergent.^[11] Analysis of the BIS obtained from cortical electroencephalographic signals in a patient under general anesthesia, could be another way to quantify nociception. It has been shown in patients receiving propofol with a BIS between 40 and 60 that a nociceptive stimulus such as tracheal intubation caused electrocortical activation with an elevation of BIS and that this change is inversely proportional to the amount of remifentanyl administered.^[12] Thus, a sudden rise in BIS, in a patient under general

Table 2
Hemodynamic variables.

	CL group n=16	VL group n=11	P
HR before tracheal intubation, beats/min	57 [44–79] (N=14)	58 [52–70] (N=9)	.92
Median value of HR for the first 5 minutes after intubation, beats/min	78 [61–87] (N=14)	57 [53–62] (N=9)	.01
Delta HR, beats/min	6.5 [0.8–19.8] (N=14)	1.0 [–6.5–4.0] (N=9)	.02
SAP before tracheal intubation, mmHg	97 [78–117] (N=13)	95.5 [82–111] (N=10)	.73
Median value of SAP for the 5 minutes after intubation, mmHg	96 [86–112] (N=12)	94 [80–95] (N=7)	.31
Delta SAP, mmHg	2.5 [–8.5–15.0] (N=12)	–4.0 [–9.0–4.0] (N=7)	.47

Group CL: conventional Macintosh laryngoscope.

Group VL: McGrath Mac videolaryngoscope.

Results are presented as medians [25th and 75th percentiles] (number of cases).

SAP: systolic arterial pressure (median of several values recorded for 5 minutes' post-intubation).

HR: heart rate (median of values recorded every minute for 5 minutes post-intubation).

Delta values are calculated as (peak value observed during the 5-minute period following tracheal intubation) – (value observed before tracheal intubation).

P values: Mann–Witney U test corrected for ties.

anesthesia, properly sedated and curarized, could indicate nociceptive stress.

We have developed an automated controller with a cascade structure including a set of rules, two proportional-integral-derivative controllers which steer the administration of propofol and remifentanyl. Two elements are key points: at any time during anesthesia the required hypnotic concentration is only that needed to complete loss of consciousness when the concentration of analgesic is appropriate, a pain stimulus induces electrocortical activation with an increase in BIS in a sedated patient. The controller continuously measures the difference between the BIS value and the setpoint of BIS (50) and its current trend and determines which drugs will be modified on the assumption that large fluctuations of BIS error are related to lack or excess of hypnosis and that small fluctuations are related to lack or excess of antinociception. Details, set of rules and gains constant of the controller are provided in the appendix of a previously published article.^[2] The controller has been used in several controlled studies, in particular a study of adult patients undergoing routine surgery with better efficacy than manual control,^[2] and studies which addressed its efficacy in some specific populations

(pediatrics,^[13] obese patients),^[14] or during some specific surgical interventions (lung transplantation,^[15] liver transplantation,^[16] and bronchoscopy),^[17] or as a method to evaluate the anesthetic effect of a conversational hypnotic session^[3] or of drugs (nitrous oxide,^[4] dexmedetomidine),^[5] or to evaluate the analgesic effect of intraoperative use of epidural analgesia.^[6]

In the present study, we made the assumption that the peak plasma concentration of remifentanyl appearing within few minutes after intubation reflects the level of nociception induced by the intubation. Moreover, the advantage of such a method is to avoid the bias linked to human intervention in the conduct of anesthesia or to fixed doses of anesthetic agents.^[18,19] Our protocol showed no difference between peak plasma concentrations of remifentanyl and of propofol following tracheal intubation suggesting that the difference in force required during the gesture has no influence on level of nociception and hypnosis. Only a transient increase in BIS was observed when a conventional laryngoscope was used.

Several studies have attempted to compare the VLS to conventional laryngoscopes, by determining the force needed to intubate for each of the devices. These studies have all shown

Table 3
Characteristics of intubation.

	CL group n=16	VL group n=11	P
Modified Cormack score, I–II/III–IV	16 (100)/0 (0)	11 (100)/0 (0)	1
Percentage of glottic opening scale, <80%/80–100%	3 (18.8)/13 (81.2)	1 (9.1)/10 (90.9)	.62
Number of attempts, 1/2	15 (93.8)/1 (6.2)	9 (81.8)/2 (18.2)	.55
Time to intubation, s	35.0 [22.0–47.0]	44.0 [36.0–61.0]	.09
Backward, upward, rightward pressure, Yes/No	8 (50.0)/8 (50.0)	1 (9.1)/10 (90.9)	.04
Sensation of abnormal force necessary to intubate	3 (18.8)/13 (81.2)	0 (0.0)/11 (100.0)	.25
Use of alternative techniques for intubation			
Stylet, Yes/No	1 (6.2)/15 (93.8)	1 (9.1)/10 (90.9)	1
LMA Fastrach, Yes/No	0 (0.0)/16 (100.0)	0 (0)/11 (100)	1
Complications			
Oxygen desaturation, Yes/No	0 (0.0)/16 (100.0)	0 (0)/11 (100.0)	1
Dental damage, Yes/No	0 (0.0)/16 (100.0)	0 (0.0)/11 (100.0)	1
Oro-pharyngeal trauma, Yes/No	0 (0.0)/16 (100.0)	0 (0.0)/11 (100.0)	1
Esophageal intubation, Yes/No	0 (0.0)/16 (100.0)	0 (0)/11 (100.0)	1
Postoperative hoarseness, Yes/No	7 (43.8)/9 (56.2)	7 (63.6)/4 (36.4)	.44
Postoperative sore throat, Yes/No	6 (37.5)/10 (62.5)	5 (45.4)/6 (54.6)	.76

Group CL: conventional Macintosh laryngoscope.

Group VL: McGrath Mac videolaryngoscope.

Results are presented as medians [25th and 75th percentiles] or number (percentages).

P values: Mann–Witney U test corrected for ties.

that the force was generally less using a videolaryngoscope, compared with a conventional Macintosh laryngoscope blade, whether on mannequins or patients.

On mannequins, Carassiti et al^[20] using film pressure transducers showed that intubation with the Glidescope (Verathon Medical France, Schiltigheim, France) required less force and a more uniform pressure distribution on the base of the tongue, compared with a conventional laryngoscope. A similar result was found by Lee et al^[21] who used piezo-resistive sensors disposed on the distal end of the blade of the laryngoscope. Finally, Caldiroli et al^[22] evaluated the muscle work required by the anesthetist during intubation, by measuring the activity of 8 muscles of the upper limb using the dynamic electromyography surface. They reported that the electrical muscular activity detected for each of these muscles was significantly lower when the Glidescope VLS was used compared with a conventional laryngoscope.

On patients, the results are broadly similar. Russell et al^[23] showed in a prospective randomized study on 24 patients American Society of Anesthesiologists I–II without risk factors for difficult orotracheal intubation well curarized before intubation, the force, measured by piezo-resistive-type sensors disposed on the distal end of the laryngoscope blade, was almost twice as low when a VLS was used compared with a conventional laryngoscope. Lee et al^[24] were interested in the risk of tooth breakage when arranging piezo-resistive sensors on the part of the blade contacting the upper incisors; the force exerted on the teeth was clearly lower when a Glidescope was used compared with a conventional laryngoscope; this study was also performed in patients without risk factors for difficult orotracheal intubation. Finally, using the same technique as Lee et al,^[24] Pieters et al^[25] compared 3 different VLS (McGrath serie5 [Aircraft Medical, Edinburgh, UK], C-Mac [Storz, Karl Storz Endoscopie, Guyancourt, France], and Glidescope [Verathon Medical France]) with a conventional laryngoscope in a large series of 141 patients having no risk of difficult intubation. Compared with a conventional laryngoscope, the force exerted on the upper incisors was consistently weaker when a VLS was used, regardless of the model chosen.

Finally, the simplest way to compare the consequence of the gesture is to analyze the hemodynamic impact. Nishikawa et al^[18] showed in a prospective randomized study of 40 patients without factors of difficult intubation significant increases in heart rate, blood pressure, and BIS when using the Macintosh blade, whereas the VLS AirWay Scope (Pentax [Tokyo, Japan]) provided no increases in either parameter. Similar results were found by Koyama et al^[19] in normotensive patients while this attenuation of the hemodynamic response to tracheal intubation was not found in hypertensive patients. As stated above these studies used predefined doses of anesthetic agents; this could probably induce a too deep level of anesthesia which persists during intubation and that can hide or limit the hemodynamic response to intubation. Using a dual closed-loop, we report a significant difference between heart rate evolution during the few minutes after intubation with a larger increase when a conventional laryngoscope is used.

Our study has obviously some limitations.

The first one is the limited number of patients. A particular finding of our study is the contrast between the comparison of the peak plasma remifentanyl concentration occurring after intubation, defined as our primary outcome, and the comparison between plasma remifentanyl and propofol concentrations during the 5 minutes after intubation (T1–T5). Both comparisons gave

nonstatistically significant differences; however, the *P* value for the comparison of the peak plasma remifentanyl concentration is .09, which suggests that the inclusion of a larger number of patients could have led to significance. One could also suggest a better usage of the automated method of drug administration which may have helped to better distinguish between the induction period, the laryngoscopy, and the intubation. It might have been interesting to induce anesthesia and then to maintain a constant dose of propofol while adjustment of remifentanyl would have followed the BIS variations. This method could have better distinguished between a lack of antinociception and a lack of hypnosis during tracheal intubation.

We found in the group of patients intubated using a conventional laryngoscope a peak plasma remifentanyl concentration (5.0 [4.2–6.6] ng/mL) much lower than that expected from previous patients (9.1 ± 2.1 ng/mL). This could be explained either by a strict selection of patients (i.e., without any risk of difficult intubation) for the present study or by the Hawthorne effect, a type of reactivity in which individuals modify or improve an aspect of their behavior in response to their awareness of being observed. This phenomenon may be an important factor affecting the generalizability of clinical research to routine practice.^[26]

Finally, the use of BIS can also be discussed. Despite recent meta-analyses which favor the use of closed-loop delivery of anesthetic agents,^[27,28] some authors have questioned their usefulness, accuracy, and risk.^[29]

5. Conclusion

In conclusion, use of a McGrath Mac videolaryngoscope compared with a conventional laryngoscope, in patients without criteria for difficult intubation, does not appear to modify the concentrations of the anesthetic agents administered by an automated system. With our limited sample size, we were not able to demonstrate that the noxious stimulus differs according to the laryngoscope used. Nevertheless, the heart rate modifications seem to be greater when a conventional laryngoscope is used.

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