THE 'ANALGOSCORE': A NOVEL SCORE TO MONITOR INTRAOPERATIVE PAIN AND ITS USE FOR REMIFENTANIL CLOSED-LOOP APPLICATION

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ASTRACT

Background: Measuring pain during general anesthesia is difficult because communication with the patient is impossible. The focus of this project is the development of an objective score ('Analgoscore'™) of intraoperative pain based on mean arterial pressure (MAP) and heart rate (HR). The Analgoscore ™ is used for closed-loop application of remifentanil.

Methods: The Analgoscore™ ranges from -9 (too profound analgesia) to 9 (too little analgesia) in increments of 1, with -3 to + 3 representing excellent pain control, -3 to -6 and 3 to 6 good pain control, and -6 to -9 and 6 to 9 as insufficient pain control. According to the zone of pain, a remifentanil infusion was either closed-loop-administered (Closed-loop Group) or manually administered by the same anesthesiologist (Control Group). The percentage of anesthetic time within the different control zones was recorded as well as the variability of MAP and HR and compared between the two groups. Data as mean ± standard deviation.

Results: In the closed-loop group, 16 patients (5 f, 11 m; age 49 ± 21 y) received a dose of remifentanil of 0.13 ± 0.08 µg/kg/min. During 84%, 14% and 0.5% of the total anesthesia time, the Analgoscore™ showed excellent, good or insufficient pain control, respectively. Artifacts were recorded only 1.5% of the time. The control group of eleven patients (4 f, 7 m; age 48 ± 17 y) received remifentanil of 0.17 (0.1) µg/kg/min. Excellent control was obtained 79% of the time, whereas good control and insufficient control yielded 16% and 0%, respectively. Artifacts were recorded 5% of the time.

Discussion: The Analgoscore™ is a novel score of intraoperative pain. Remifentanil was successfully closed-loop-administered.

INTRODUCTION

Pain control during general anesthesia is not easy since the patient cannot talk. However, indirect parameters, such as reactions of the autonomic nerve system, for example sweating, or changes in heart rate or arterial pressure can be used to assess pain [1-6]. Opioids, used during surgery for pain control, are known to effectively block changes in heart rate or blood pressure during periods of surgical stimuli [7]. Although heart rate or blood pressure have been used in surgeries [8-13] to assess pain – as reflected in hemodynamic stability– there is an absence of studies to establish any kind of 'intraoperative pain score', equivalent to the visual pain score widely used to assess pain in the conscious patient. In addition, those studies used either heart rate or blood pressure but not a combination of both [12,14,15]. Thus, the focus of this project is the development of a novel, objective score (called Analgoscore™) of intraoperative pain using MAP *and* HR to which an expert-based, adaptative system is linked to administer remifentanil.

METHODS

<u>Analgoscore algorithm</u>

Depending on the type of surgery and the patient general condition, the anesthetist defined target values for MAP and HR during surgery. The MAP, measured non-invasively, and the HR are acquired using a vital sign monitor (Welch Allyn, Inc., Skaneateles Falls, NY). Using these target values of MAP and HR, the

the Analgoscore™ defines three zones as shown in Table 1. The range of the Analgoscore is defined from -9 (too profound analgesia) to 9 (insufficient analgesia) in increments of 1. Three control regions were defined with -3 to +3 representing excellent pain control, -3 to -6 and 3 to 6 good pain control, and -6 to -9 as well as 6 to 9 inadequate pain control. The score is calculated by comparing the offset percentage between target and measured values using expert based rules. The algorithm modeling this procedure is illustrated in figure 1 and is repeated every minute throughout the surgery to adjust the infusion rate. Several correction factors then act to modify and validate a new infusion rate. The amount of remifentanil infused is calculated dynamically based on algorithms according to the score. Since MAP or HR can be influenced by other reasons than changes in analgesia, hypovolemia was defined as a predominant increase of HR with or without decrease of MAP, and vagal reactions (e.g. caused by pneumoperitoneum during laparoscopic surgery) defined as a predominant decrease of HR with or without increases of MAP. When such situations occurred, the clinician was advised and a pre-defined infusion rate of remifentanil 0.01 µg/kg/min administered.

Table 1: Rules for score determination

MAP **HR**	<20%	<15%	<10%	<5%	**MAP**	>5%	>10%	>15%	>20%
<35%	-9	-8	-6	-5	-4	Vagal Reaction			
<25%	-8	-7	-5	-4	-3				
<15%	-6	-5	-4	-3	-2				
<10%	-5	-4	-3	-1	-1				
HR	-4	-3	-2	-1	0	1	2	3	4
>10%	Hypotension caused by volume depletion				1	1	3	4	5
>15%					2	3	4	5	6
>25%					3	4	6	7	8
>35%					4	5	6	8	9

MAP: Mean arterial pressure
HR: Heart rate

Table 2 shows how the remifentanil rate is modified by a corrector factor (CF) according to the generated Analgoscore™. This factor is also combined to K1 and K2 factors (factors to account for trends in offset from target values over time) to engender the new remifentanil infusion rate as follows:

$$NewInfusion = OldInfusion \times CF \times K_1 \times K_2 \qquad (1)$$

Where:

$$K1 = \begin{cases} 2 & MeanSlope > 1 \\ 1.25 & 0.5 < MeanSlope \leq 1 \\ 1.10 & 0 < MeanSlope \leq 0.5 \\ 1 & MeanSlope = 0 \\ 0.90 & -0.5 < MeanSlope \leq 1 \\ 0.75 & -1 \leq MeanSlope < -0.5 \\ -1 & MeanSlope < -1 \end{cases} \qquad (2)$$

And

$$K2 = \begin{cases} 1.5 & 6 \leq Score < 9 \\ 1.25 & 3 \leq Score < 6 \\ 1 & 0 \leq Score < 3 \\ 0.75 & -3 \leq Score < 0 \\ N/A & -9 \leq Score < -3 \end{cases} \qquad (3)$$

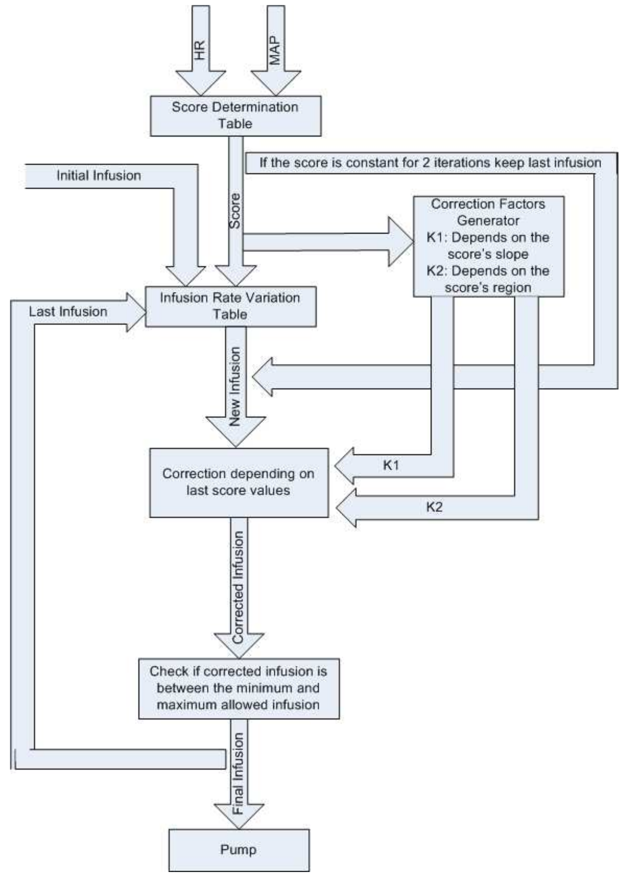

Figure 1: Closed-loop algorithm

Remifentanil is administered using a Graseby 3400 infusion pump (Graseby Medical, Watford, UK) linked to a notebook computer via a serial RS232 port. Algorithms were developed using LabVIEW National Instruments (National Instruments Corporation, Austin, Texas) and with Visual Basic (Microsoft Corporation, Seattle, Washington) and used to control the infusion pump through a second serial port.

Table 2: Infusion rate variation

Analgoscore	**Infusion Modification**	**CF**
-9 to -2	No infusion	
-1,0, 1	No change	1
2	↑20%	1.2
3	↑30%	1.3
4	↑40%	1.4
5	↑50%	1.5
6	↑60%	1.6
7	↑70%	1.7
8	↑80%	1.8
9	↑90%	1.9

CF: Correction factor

Clinical trial

After having obtained written patient consent, 27 patients undergoing general and orthopedic surgery of moderate pain intensity were included. In all patients, general anesthesia was induced using fentanyl 5 µg/kg, propofol 1.5 mg/kg and rocuronium 0.3 mg/kg after which a laryngeal mask airway was inserted. MAP and HR were determined once every min and an Analgoscore reading obtained at this time interval. MAP and HR were considered 'stable' if they were within 20% of the target value. The percentage of time during which the Analgoscore readings were within -3, 3, or -6,-3 and 3,6, or -9,-6 and 6,9 were calculated. Remifentanil was administerd in closed loop fashion (N=16).

In a control group of 11 patients, the Analgoscore^{TM} was calculated and displayed; an anesthesiologist with more than 10 years of experience of continuous administration of remifentanil for surgery and not involved in the study infused remifentanil to maintain the Analgoscore^{TM} within the range of -3 to 3.

Using the method of Varvel et al. [20], the controller performance was obtained by measuring the variation of MAP and HR from the target values specified by the anesthetist. The performance error (PE) is given by:

$$PE = \frac{\text{(Measured Value - Target Value)}}{\text{Target Value}} \times 100 \quad (4)$$

Consequently [21], the median performance error (MDPE) which is a measure of bias and shows if the measured variables are above or below the target values is calculated:

$$MDPE_i = Median\{PE_{ij}, j = 1,..., N_i\} \quad (5)$$

where N_i if the number of acquisitions for the ith patient and j is the acquired sample.

As for the median absolute performance error (MDAPE), it reflects the inaccuracy of the control system for the ith patient:

$$MDAPE_i = Median\{|PE|_{ij}, j = 1,..., N_i\} \quad (6)$$

In this context, wobble is a measure of the variability of the PE_{ij} in the i_{th} individual:

$$Wobble_i = Median\{|PE_{ij} - MDPE_i|, j = 1,..., N_i\} \quad (7)$$

As for divergence, it reflects the evolution of the controller's performance through time (worsening or improvement). It is the slope obtained from linear regression of the subject's absolute PE against time. A positive slope indicates a gradually widening gap between the measured and targeted values whereas a negative value shows that the measured value tends to converge to the target values.

Parameters between the two groups are compared using the Mann-Whitney U test for continuous data and the Chi-square test for categorical data; $P<0.05$ considered statistically significant.

RESULTS

Sixteen patients (5 f, 11 m; age: 49 ± 21 y; weight: 70 ± 11) underwent anesthesia of mean duration of 111 ± 44 min received a mean dose of remifentanil of 0.13 ± 0.08 µg/kg/min. The Analgoscore showed excellent control during 84%, good control during 14% of the time, insufficient control was observed only 0.5% of the surgery time while 1.5% of the time was associated to other causes (i.e. with hypovolemia or vagal-type reactions).

In the control group of eleven patients (4 f, 7 m; age 48 ± 17 y) underwent anesthesia of 110 (25) min with remifentanil infusion of mean 0.17 (0.1) µg/kg/min. Excellent control was obtained 71% of the time, whereas good control and insufficient control yielded 23% and 0% respectively. Artifacts were recorded 6% of the time (Figure 2).

The results of the MDPE, MDAPE, divergence and wobble for the MAP and HR are shown in Tables 3 and 4, respectively, and were not different between the groups.

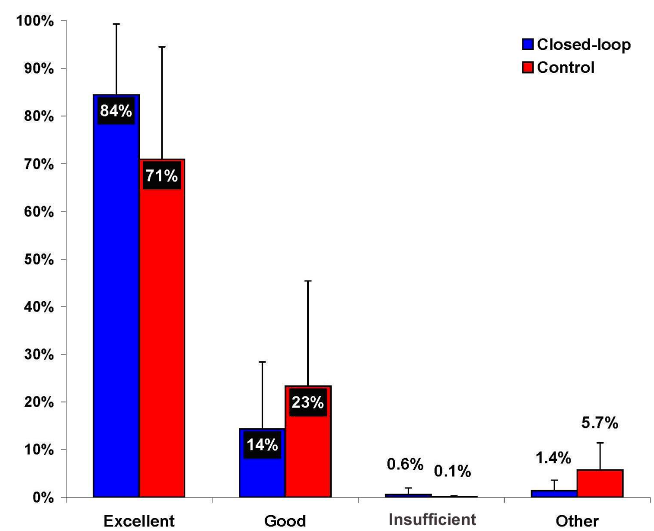

Figure 2: Analgesia control over time; Excellent represents an Analgoscore between -3 and 3; Good: between 3 and 6 or -6 and -3; Insufficient: between 6 and 9 or -9 and -6; Other represents vagal reactions or hypovolemia.

Table 3: Performance indices for MAP

	Closed-loop Group	Control Group	P value
MDPE [%]	-0.99 ± 10.01	-0.29 ± 11.83	0.856
MDAPE [%]	9.73 ± 4.95	11.88 ± 7.55	0.429
Divergence [%.s^{-1}]	0.004 ± 0.12	-0.08 ± 0.20	0.481
Wobble [%]	6.17 ± 3.39	7.99 ± 2.66	0.056

MAP = mean arterial pressure; MDPE = median performance error; MDAPE = median absolute performance error

TABLE 4: Performance indices for HR

	Closed-loop Group	Control Group	P value
MDPE [%]	-4.36 ± 5.12	-1.27 ± 6.30	0.229
MDAPE [%]	6.28 ± 3.76	6.80 ± 3.87	0.743
Divergence [%.s^{-1}]	-0.022 ± 0.087	0.053 ± 0.24	0.512
Wobble [%]	3.28 ± 1.84	4.36 ± 2.37	0.182

HR = heart rate; MDPE = median performance error; MDAPE = median absolute performance error

DISCUSSION

Assessing pain during general anesthesia is not an easy task. Communication with the patient is impossible, indirect parameters have to be used to estimate the amount of pain. The interpretation of these parameters and the subsequent administration of analgesics is based on subjective decision-making of each anesthesiologist: it is based on his experience, his anesthetic preferences, his knowledge of pharmacokinetics and specific, patient-related data, such as preoperative blood pressure or surgery-related parameters, such as the degree and timing of surgical stimuli.

More objective decision-making has been proposed; however, only one study tested the control of MAP and HR in clinical conditions. Carregal et al. [23] proposed a closed loop system using HR and MAP to regulate alfentanil infusions. In comparison to the results of Carregal et al. [23], Analgoscore provided a better hemodynamic stability with MAP within 10% of target value in 91% of the surgical total time of 1772 minutes and HR within 10% of target value in 99% of the total control time. The better hemodynamic stability might be due to better controller performance as well as the use of the more rapid acting remifentanil.

More complex systems integrating depth of anesthesia, analgesia and muscle relaxation are planned to develop more intelligent automated anesthesia application systems.

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