



## DETERMINATION OF THE EFFECTIVE DOSE OF SEVOFLURANE ABLE TO BLOCK HYPERTENSIVE RESPONSE DURING LAPAROSCOPY

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### ABSTRACT

**Background:** Vasopressin (VP) was recently identified as a major modulator of hypertension during laparoscopy (LAP). We searched for the effective dose (ED) of sevoflurane (S) with and without N<sub>2</sub>O able to control hemodynamic response (CHR) during LAP. **Material and Methods:** The study was developed in five Mexican states, including ASA I patients divided in two groups: G I: S plus 60% N<sub>2</sub>O (n=88) and G II: S alone (n=72). Conventional monitoring along BIS was used and basal data were recorder. Blood samples for nor epinephrine (NE) determination were drawn basal, 3´ after endotracheal intubation and 10´ after sustained insufflation (SI) and for VP basal, after hydration and 3´ after SI. The range of S for ED determination was 0.5 to 4% for both groups, as measured in Et concentration. Identification of the ED<sub>50-95</sub> of S for CHR during LAP was done using Waud´s method. **Results:** No demographic differences were observed between groups except for gender. ED<sub>50</sub> of S for G I was 1.5 +/- 0.3 and for G II 2.0 +/- 0.32. ED<sub>95</sub> were 2.0 +/- 0.4 and 3.0 +/- 0.27 respectively. No differences in hemodynamic behavior were observed for ED<sub>50</sub> or <sub>95</sub> between groups. Plasma VP levels were significantly lower in N<sub>2</sub>O supplemented patients (6.4 vs. 97.3 pg/ml). Adequacy of anesthetic depth was observed in all cases for ED<sub>50-95</sub>. **Discussion:** The ED<sub>50-95</sub> of S for CHR during LAP with and without N<sub>2</sub>O are described. A different dose of the one described for open procedures is reported. Neuroendocrine behavior is likely to be the explanation for this difference.

**Keywords:** Laparoscopy, sevoflurane, vasopressin, nor epinephrine, anesthetic techniques.

### RESUMEN

**Antecedentes:** Recientemente se ha identificado a la vasopresina (VP) como modulador de la respuesta hipertensiva durante laparoscopia (LAP). Buscamos la dosis efectiva (ED) de sevoflurano (S) con y sin N<sub>2</sub>O capaz de controlar la respuesta hipertensiva (CHR) durante LAP. **Material y Métodos:** El estudio fue desarrollado en cinco estados Mexicanos, incluyendo pacientes ASA I en dos grupos: G I: S más 60% de N<sub>2</sub>O (n=88) y G II: S solo (n=72). Se empleó monitoreo convencional junto con BIS capturándose los datos basales. Se obtuvieron muestras sanguíneas para determinación de norepinefrina (NE) basal, 3´ después de intubación y 10´ después de insuflación sostenida (SI) y de VP basal, después hidratación y 3´ después de SI. El rango de S para la determinación de la DE fue de 0.5 a 4% para ambos grupos, de acuerdo a la concentración al final de la espiración. La identificación de la ED<sub>50-95</sub> de S para CHR fue realizada con el método de Waud. **Resultados:** No se encontraron diferencias demográficas entre los grupos a excepción del sexo. La ED<sub>50</sub> de S para el G I fue de 1.5 +/- 0.3 y para el G II 2.0 +/- 0.32. La ED<sub>95</sub> fue de 2.0 +/- 0.4 y 3.0 +/- 0.27 respectivamente. No se observaron diferencias entre grupos en el comportamiento hemodinámico para la ED<sub>50-95</sub>. Los niveles plasmáticos de VP fueron significativamente menores en los pacientes suplementados con N<sub>2</sub>O (6.4 vs. 97.3 pg/ml). El plano anestésico fue adecuado en todos los casos con ED<sub>50-95</sub>. **Discusión:** Describimos las ED<sub>50-95</sub> de S con y sin N<sub>2</sub>O para CHR durante LAP. Reportamos una dosis distinta a la referida para los procedimientos abiertos. La explicación de esta diferencia parece encontrarse en el comportamiento neuroendocrino.

**Palabras clave:** Laparoscopia, sevoflurano, vasopresina, norepinefrina, técnicas anestésicas.

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### BACKGROUND

The wide application of laparoscopic techniques has generated several investigations conducted to properly identify the physiological changes associated.

Hemodynamic changes, specifically hypertension, have been focused as related to mechanical compromise induced by CO<sub>2</sub> insufflation (CO<sub>2</sub>); nevertheless, the role of chemical modulators of hypertension and their modification related with CO<sub>2</sub> in presence of a certain anesthetic technique, has not been extensively studied.<sup>1-3</sup>

The analysis of the role of potential modulators of hypertensive response during CO<sub>2</sub> include: ACTH, AVP, catecholamines and cortisol.<sup>4</sup>

In recent reports, the role of vasopressin (VP) as determinant of hypertension and increase of systemic vascular resistances in a response to CO<sub>2</sub>, has been highlighted.<sup>5</sup> It is now known that an early peak release of VP is observed approximately 3 minutes after sustained insufflation; also it is known that a further and late peak of norepinephrine is observed 10 minutes after sustained CO<sub>2</sub>. Considering these findings a difference is observed between open surgery and laparoscopic

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procedures, situation conducting us to redefine the current anesthetic management for these different surgical stimulus.

This study was designed to identify the dose of sevoflurane with and without nitrous oxide able to block the hemodynamic response to abdominal insufflation, considering a different endocrine behavior for laparoscopic procedures as compared with open surgery.

## MATERIAL AND METHODS

We designed a multicentric study including 5 Mexican states at different altitudes, to determine the dose of sevoflurane (S) able to block the hemodynamic response (hypertension and tachycardia) to abdominal CO<sub>2</sub>.

After informed consent and after previous approval by the Ethics Committees of all the participant Institutions, a total of 160 patients randomly allocated in one of two groups:

Group I (S + 60% N<sub>2</sub>O): n= 88

Group II (S alone): n= 72

All patients were included according the following criteria: Both sexes, ages between 18 and 60 years, ASA physical status I, body mass index (BMI) not higher than 30, presence of gall bladder stone disease. Exclusion criteria included: Patients with ASA physical status classification II to V, BMI higher than 30, allergy history to any drug used in the study.

Once included all patients showing hypotension or requiring vaso active drugs of any kind were removed from the study. Patients with data suggesting cardiac compromise such as: capnography lecture lower than 28, mean arterial pressure lower than 60 mmHg, heart rate lower than 50 or BIS index higher than 70% were also removed from the study.

All patients had a minimum of 8 hours fasting period prior to surgery; pre anesthetic management included placement of an IV line for fluids and another for sampling and pre medication with ranitidine and metoclopramide. In no case anxiolysis was pharmacologically induced.

At the arrival to the operating room monitoring was instituted, including: continuous electrocardiography, non invasive arterial pressure, pulse oximetry. Other monitoring devices included: Et CO<sub>2</sub> measurement, Et anesthetic gas analysis, and also a bispectral analysis (BIS) sensor was placed in the frontal region.

Once monitored basal vital signs measurement were recorded (T<sub>0</sub>) and blood samples were obtained for determination of basal levels of vasopressin (VP) and norepinephrine (NE) (H<sub>0</sub>).

Later, hydration was obtained with Hartman's solution (10 ml Per Kg of ideal weight) using a pressure bag set at 100 mmHg in order to deliver the entire volume in approximately 15 minutes. After hydration another blood sample for the determination of VP was obtained (H<sub>1</sub>).

Vital signs were then recorded at the following periods: T<sub>1</sub> (after hydration), T<sub>2</sub> (3 minutes after endo tracheal tube placement), T<sub>3</sub> (1 minute before reaching 15 mmHg of intra abdominal pressure), T<sub>4</sub> (3 minutes after reaching and sustaining 15 mmHg of intra abdominal pressure), T<sub>5</sub> (10 minutes after reaching and sustaining 15 mmHg of intra abdominal pressure).

Blood samples were drawn for further hormonal determination with the following sequence: *Vasopressin*: H<sub>3</sub> (3 minutes after reaching and sustaining 15 mmHg of intra abdominal pressure).

*Norepinephrine*: H<sub>2</sub> (3 minutes after endo tracheal tube placement), H<sub>4</sub> (10 minutes after reaching and sustaining 15 mmHg of intra abdominal pressure).

Laboratory processing for hormonal determination was done on a blind fashion.

Induction of anesthesia was done according to the following sequence: cefuroxime 1.5 gr single dose, thiopental 5 mg • Kg of ideal weight, atracurium: pre curarization 0.1 mg • Kg of ideal weight and total dose of 0.5 mg • Kg of ideal weight one minute after pre curarization. A fentanyl loading dose of 3 µgr • Kg of ideal weight was given, and in a time period not exceeding 30 minutes a 3 µgr • Kg of ideal weight per hour fentanyl infusion was initiated. After obtaining a BIS level under 50% and after detecting the absence of response to single twitch, an endo tracheal tube was placed.

Each patient was allocated into a dose subgroup ranging from 0.5 to 4% of sevoflurane, determined by Et concentration of the gas either with or without N<sub>2</sub>O supplementation; every subgroup was conformed by 16 patients and cardiovascular response goals were searched. If hypertension or tachycardia were observed, the patients were removed from the protocol and considered a failure of the dose of S to control hemodynamic response being managed according the criteria of the anesthesiologist in charge.

In all cases the end tidal concentration of the gas must have been reached when the insufflation was achieved and sustained; also an EtCO<sub>2</sub> of 28 and a BIS level ranging between 50 and 70% was reached.

In all cases blood samples were processed by an investigator unaware of the anesthetic technique and also the clinical investigators were unaware of the hormonal levels until the end of the study.

The study was considered concluded after 10 minutes after sustained insufflation and after obtaining the last blood sample.

Determinations of vasopressin (VP) and norepinephrine (NE) were done at the predetermined periods only in 25 patients per group when ED<sub>95</sub> was identified.

**STATISTICAL ANALYSIS**

All results were expressed as mean +/- SD. Demographic differences were analyzed using Student t Test. Differences between groups were analyzed using ANOVA. Identification of ED 50 of S was done according the method described by Waud<sup>6</sup>. P values < 0.05 were considered significant.

**RESULTS**

No demographic differences were observed for weight, body mass index, or height. The only difference was a significant female predominance (Group I: M 31- F 57 and Group II: M 23 F 49) (Table 1).

Table I. Demographic data.

PARAMETER	WITHN <sub>2</sub> O(N=88)	WITHOUTN <sub>2</sub> O(N=72)	PVALUE
WEIGHT(KG±SD)	68.3±12.7	64.2±10.94	0.3
HEIGHT (M±SD)	1.6±0.05	1.6±0.08	0.8
REALWEIGHT(KG±SD)	54.5±8.6	56.2±9.18	0.5
BODYMASSINDEX	26.2±3.9	24.9±3.6	0.3
AGE(YEARS±SD)	37.05±10.1	36.3±12.5	0.8
GENDER (M/F)	31 / 57	23 / 49	

Considering the doses, patients receiving N<sub>2</sub>O as part of the anesthetic mixture showed a sevoflurane ED<sub>50</sub> (dose able to block hypertensive response in 50% of the cases) of 1.5±0.3 and patients not using N<sub>2</sub>O showed a sevoflurane dose of 2.0%±0.32 for the same parameter. Results for ED<sub>95</sub> were 2.0±0.4 y 3.0±0.27 respectively (Figures 1 and 2).

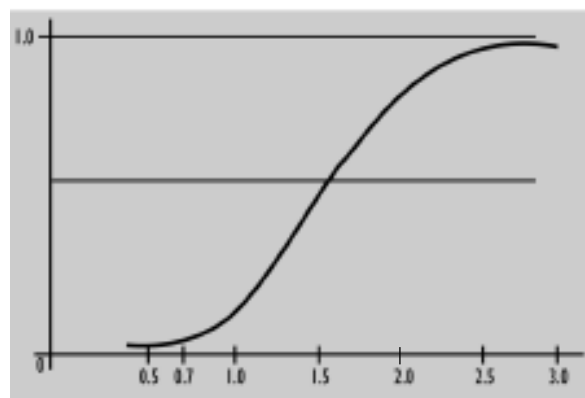
MAP behavior for patients receiving ED<sub>95</sub> of S is shown in figure 3. The respective values for each surgical moment in group I are as follows: T0, 88 ±13.5; T1, 90.5±9.7; T2, 73.2±9.9; T3, 63.5±6.5; T4, 56.5±21.4; T5, 71.6±18.9 and for group II: T0, 86.2±5.1; T1, 97.7 ±4.5; T2, 71 ±15.0; T3, 75.3 ±6.3; T4, 80±33.4; T5, 95±4.6. No statistical difference was obtained at any moment neither within the group or between them (T0: 0.8; T1: 0.25; T2: 0.83; T3: 0.06; T4: 0.36; T5: 0.07 between groups). A tendency to increase MAP values was observed starting on T3 for group II; this tendency was the same for group I starting on T5; no hypertension definition was reached at any moment for both groups.

No differences on heart rate were observed at any surgical period and with any dose subgroup.

Vasopressin determinations showed a significant difference at T3 for patients not receiving Nitrous oxide (GI: 6.4 pg/ml and GII: 97.3 pg/ ml) (p= 0.0001). With respect to norepinephrine, values at all times showed no statistical differences.

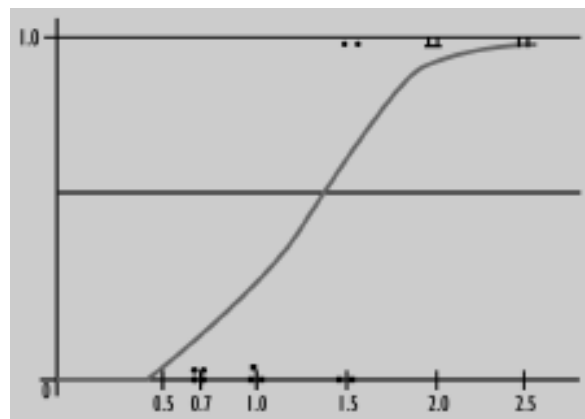
Considering BIS, it is important to notice the fact that in both groups and for ED<sub>95</sub> the mean BIS value was 31% since T3 (p=0.43). At the beginning of the procedure BIS values were above 95%. At no point a significant difference was obtained between groups.

Figure 1



Patients receiving sevoflurane without N2O (n=72)

Figure 2



Patients receiving sevoflurane with N2O (n=88)

**DISCUSSION**

Determination of ED<sub>50</sub> and <sub>95</sub> of sevoflurane able to block hypertensive response during laparoscopy is described.

Controversial data exist concerning neuro-endocrine behavior during laparoscopic procedures, but there is enough evidence pointing to a completely different pattern in comparison to open procedures.<sup>2,4,5,7,9</sup> As mentioned previously recently, a special vasopressin release pattern has been described,<sup>5</sup> and based on this experience we hypothesized the existence of a different anesthetic dosage for laparoscopic procedures.<sup>5</sup>

This study was based on a previous report done by Roizen et. al.<sup>8</sup> who described the effective doses for the control of adrenergic response to skin incision (MAC

BAR); evidently, as mentioned earlier, considering the actual knowledge, a different alveolar concentration able to block hypertensive response of the one currently available, could be hypothesized.

We found  $1.5 \pm 0.3\%$  of sevoflurane with 60% nitrous oxide as  $ED_{50}$  and  $2.0 \pm 0.4$  without nitrous oxide. Due to the design of the study several considerations can be made; in order to assure anesthetic depth adequacy, we supplemented the anesthetic management both with fentanyl and nitrous oxide.

Recently, Katoh et al.<sup>9</sup> identified the MAC for S is 1.77 % with a 40% reduction adding fentanyl (approximately 1.5 ng/ml); the MAC 95 was found in 2.21 %. Therefore it is interesting to notice that in our study, for S alone, the identified dose to prevent hypertension in 50% of the cases was 2%, amount which we expected higher even in presence of fentanyl; this finding is even more interesting in the group supplemented with nitrous oxide.

We consider the explanation might be found in the blockade of plasma increment of VP found in group I.

The dose able to block hypertensive response in 50% of the cases in group I was 1.5% and this correlates with 31% of BIS activity. This observation supports the observations made by Dr. Glass<sup>11</sup> in terms of administering hypnotic (in our case sevoflurane) concentration equal to its MAC awake value and an opiate (or analgesic). Nevertheless, in close procedures, the amount of opiate should be analyzed considering the important role of VP.

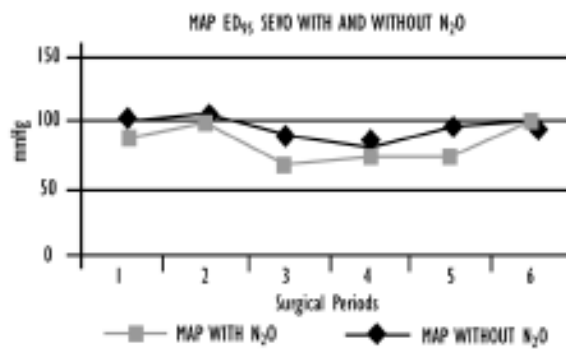
In our study we detected an unexpected finding, which was the capability of  $N_2O$  to reduce VP plasma levels during laparoscopy. Further analysis of this finding will be published in the future, but it is important to notice that this might be the reason for obtaining the important S requirement reduction and not on catecholaminergic basis.

On the other hand, we consider that the fact of having used fentanyl in an homogeneous pattern explains the MAC BAR reduction of S and the lack of statistical difference between groups along with the slight non significant increment of NE level 10 minutes after insufflation.

To notice is the fact that in both groups and at all doses no heart rate increment was observed. This might be related to the reported depressant effect of sevoflurane of the baroreflex-sympathetic reflex system and of the baroreflex control of heart rate<sup>16</sup>.

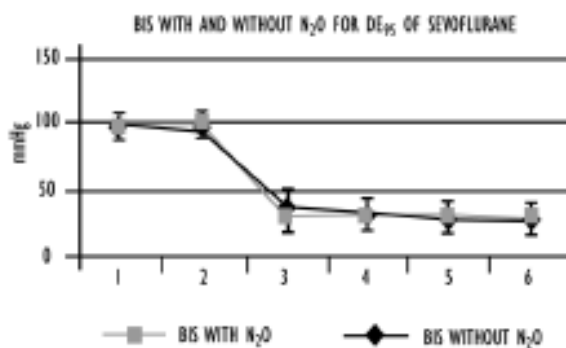
Finally it is very interesting to notice that even at  $ED_{50}$  the BIS activity was importantly depressed. In our point of view this observation supports the fact of reaching lower alveolar concentrations, using as in this report, a double pathway analgesic strategy, e.g.: nitrous oxide – fentanyl. Specifically considering  $N_2O$ , recent evidence, along with our findings, confers the gas an important role for laparoscopic procedures<sup>18</sup>.

Figure 3



Mean Arterial Pressure at different surgical periods with  $ED_{95}$  of Sevoflurane. No statistical difference was observed at any moment.

Figure 4



Bis levels for both groups. Legend: BIS con = Bispectral index using  $N_2O$ ; BIS sin = Bispectral index not using  $N_2O$ .

It is important to outline the fact that, in the present experience, we did not find a nitrous oxide effect on BIS, as suggested by the lack of difference of BIS levels between groups for the same  $ED_{50-95}$  of S. This finding is concordant with reports of other investigators<sup>19</sup>.

In conclusion, we are describing the doses of  $N_2O$  supplemented and non supplemented sevoflurane-fentanyl based anesthetic scheme for the management of laparoscopic cholecystectomy.

Further research is required in order to explain the exact neuroendocrine behaviour to clarify the mechanisms of general anesthesia for the procedures using  $CO_2$ .

## ANNEX I

Operative Definitions: The following definitions were adopted for cardiovascular response:

**Hypotension:** MAP < 50 mmHg or less than 10% of the basal value.

**Hypertension:** MAP > 110 mmHg or more than 10% of the basal value.

**Bradycardia:** Heart rate < 40 bpm or less than 10% of the basal value.

**Tachycardia:** Heart rate > 120 bpm or more than 10% of the basal value.

**Success criteria:** Success criteria for control of the cardiovascular response to peritoneal insufflation:

- 1) MAP increase of no more than 10% of the basal value after insufflation of the peritoneal cavity.
- 2) Heart rate increase of no more than 10% of the basal value after insufflation of the peritoneal cavity.

Adequacy of anesthetic depth was defined as follows:

- 3) BIS level ranging between 50 and 70% during the procedure.

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