

# REMIFENTANIL PREVENTING HEMODYNAMIC CHANGES DURING LAPAROSCOPIC ADRENALECTOMY FOR PHEOCHROMOCYTOMA

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## Summary

In this prospective case-series study, a balanced anesthetic scheme of sevoflurane in nitrous oxide supplemented with remifentanil and sustained neuromuscular block was applied in nine patients scheduled for laparoscopic adrenalectomy for pheochromocytoma. Laparoscopic adrenalectomy to treat pheochromocytoma results in marked catecholamine release during pneumoperitoneum and tumor manipulation. Remifentanil infusion was adjusted to maintain systolic arterial pressure between 120-170 mmHg. Increased infusion rate of remifentanil was used (up to 3 µg/kg/min) to prevent and treat marked hemodynamic changes from catecholamine release during tumor manipulation. Hypotension after tumor removal was treated with additional colloids fluids and decreasing the remifentanil infusion rate by 25-50%.

## Introduction

Recently the use a laparoscopic approach has been used for resection of pheochromocytoma<sup>1,2</sup>. Anesthesia for pheochromocytoma remains a

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clinical challenge. Laparoscopy further complicates the management of anesthesia. The hemodynamic and catecholamine responses to laparoscopic adrenalectomy have been well described<sup>3,4,5</sup>. The increase in intraabdominal pressure during conventional pneumoperitoneum is sufficient to trigger catecholamine release, further aggravating hemodynamic changes. Moreover, and more particularly, the resection of pheochromocytoma induces marked hemodynamic changes and catecholamine release. The times of peak hemodynamic response and catecholamine secretion are during the creation of pneumoperitoneum and during tumor manipulation<sup>3,4</sup>. A combination of intravenous and inhaled drugs is commonly used to maintain hemodynamic stability during the intraoperative period. Opioid analgesics are the most commonly used drugs to attenuate acute intraoperative hemodynamic responses. Remifentanyl, a novel esterase-metabolized opioid, rapidly and effectively suppress acute intraoperative hemodynamic responses without prolonging recovery time<sup>6,7</sup>.

Resections of pheochromocytoma require more operative time and demand rapid emergence from anesthesia and responses due to the concern of persistent hypotension following adrenal vein ligation and a consequent decrease in circulating catecholamines. This hypotension is presumed to be due to down-regulation of sympathetic alpha- and beta-receptors from prolonged sympathetic nervous stimulation. We choose not to compound this down-regulated state by affecting persistent sympatholysis with longer acting anesthetic and analgesic agents.

The present study was undertaken with the aim to assess the safety, efficacy, and morbidity of laparoscopic adrenalectomy for suspected pheochromocytoma using balanced anesthesia by continuous infusion of remifentanyl and sevoflurane in nitrous oxide and sustained neuromuscular block.

### **Patients and Methods**

This is a prospective study of case series performed between June 1998-November 2002. After approval of our Institutional Ethics

Committee and written patient informed consent, nine patients scheduled for laparoscopic adrenalectomy for pheochromocytoma were reviewed.

Preoperative pharmacological control of the adverse effects of circulating catecholamines was essential. The main objective was to control blood pressure, heart rate and arrhythmias and, especially, to allow blood volume to be restored to normal. Patients were receiving phenoxybenzamine to achieve adequate  $\alpha$ -blockade, optimal hydration prior to surgery and beta-blockers for 2-3 weeks. Individual antihypertensive therapy that were maintained until the morning of surgery included a combination of drugs such as calcium-channel blockers, angiotensin-converting enzyme inhibitor, nitrate, and  $\beta$ -blockers.

We used the same anesthetic protocol in all patients. On the day of surgery patients received their usual antihypertensive medication and oral premedication with temazepam 20 mg. Prior to induction of anesthesia lactated Ringer's solution 8-10 ml/kg was infused as loading volume.

Anesthesia was induced with 2  $\mu$ g/kg fentanyl and propofol 1.5-2 mg/kg and the trachea was intubated by 0.5 mg/kg cis-atracurium and was maintained with sevoflurane at end-tidal concentration of 1.0-1.5 MAC in 50% N<sub>2</sub>O/O<sub>2</sub>. Muscle relaxation was achieved by a continuous infusion of cis-atracurium. A continuous infusion 0.15-0.25  $\mu$ g/kg/min of remifentanyl started immediately after intubation. A central venous catheter was introduced via right jugular vein, and an arterial line was inserted into the radial artery.

After induction of anesthesia, patients were positioned in lateral position and pneumoperitoneum was created by trans-abdominal approach using a CO<sub>2</sub> insufflator. During procedure the intra-abdominal pressure was maintained at 12-14 mmHg. Ventilation was adjusted to keep ETCO<sub>2</sub> between 32-37 mmHg by changing tidal volume. During the procedure, systolic arterial blood pressure was maintained within  $\pm$  30% of baseline values by adjusting the infusion rate of remifentanyl which was increased or decreased by steps of 25% of the initial infusion rate.

All hemodynamic and ventilatory data were measured and calculated

at the following time points: before induction of anesthesia ( $T_0$ ), after induction of anesthesia ( $T_1$ ), with the patient at lateral position ( $T_2$ ), 5 min ( $T_3$ ) and 20 min after insufflation ( $T_4$ ), 5 min before adrenal vein ligation ( $T_5$ ) and 5 min after adrenal vein ligation ( $T_6$ ), after CO<sub>2</sub> deflation ( $T_7$ ) and in the recovery room ( $T_8$ ).

According to the protocol a rescue nitrate agent was readily prepared in case systolic blood pressure exceeded 180 mmHg, and 0.25-0.5 mg IV bolus doses of atenolol to treat tachycardia, when it was greater than 120 bpm. Patients received colloid solution before adrenal vein ligation due to a concern about hypotension as a consequent decrease in circulating catecholamines. For persistent bradycardia (HR<45 bpm), the remifentanil infusion rate was decreased by 50%, and 0.01 mg/kg intravenous atropine was administered.

Postoperatively, after extubation, patients were transferred and monitored to the intensive care unit until the next morning.

## Results

Patients' characteristics and surgery data are shown in Table 1.

*Table 1*  
*Patient and surgery Data*

n = 9	Mean ± SD (range)
Age (yr)	42.5 ± 5.7 (23-64)
Sex ratio (M/F)	6/3
Weight (Kg)	71.5 ± 6.5 (47-96)
Height (cm)	163.5 ± 3.4 (150-178)
Surgery time (min)	187 ± 18 (165-235)
Blood loss (ml)	205 ± 23 (125-280)

Time course of changes in mean arterial pressure (MAP), heart rate (HR), central venous pressure (CVP) and infusion rate of remifentanil during pneumoperitoneum and pheochromocytoma resection are shown in Table 2.

*Table 2*  
*Hemodynamic changes and infusions rates during transabdominal*  
*adrenalectomy in lateral position (n = 9).*

Time	MAP (mmHg)	HR (bpm)	CVP (mmHg)	Remifentanil ( $\mu\text{g}/\text{Kg}/\text{min}$ )
T <sub>0</sub>	95 $\pm$ 17	74 $\pm$ 14		
T <sub>1</sub>	72 $\pm$ 13	66 $\pm$ 11	9.2 $\pm$ 0.8	0.15 $\pm$ 0.05
T <sub>2</sub>	74 $\pm$ 14	64 $\pm$ 13	9.3 $\pm$ 0.9	0.25 $\pm$ 0.05
T <sub>3</sub>	103 $\pm$ 12	65 $\pm$ 10	12 $\pm$ 0.8	0.5 $\pm$ 0.04
T <sub>4</sub>	97 $\pm$ 14	66 $\pm$ 11	13 $\pm$ 0.5	0.7 $\pm$ 0.06
T <sub>5</sub>	98 $\pm$ 10	79 $\pm$ 10	14.9 $\pm$ 0.8	1.7 $\pm$ 0.09
T <sub>6</sub>	99 $\pm$ 12	76 $\pm$ 0.8	14.3 $\pm$ 0.7	0.35 $\pm$ 0.06
T <sub>7</sub>	74 $\pm$ 11	64 $\pm$ 12	13 $\pm$ 0.6	0.15 $\pm$ 0.02
T <sub>8</sub>	75 $\pm$ 13	68 $\pm$ 10	10 $\pm$ 0.5	0.05 $\pm$ 0.03

After induction of anesthesia, the mean arterial pressure significantly decreased, while heart rate mildly decreased. At intra-abdominal CO<sub>2</sub> insufflation, the MAP and CVP significantly increased as expected. Titration of remifentanil (0.5-1.0  $\mu\text{g}/\text{kg}/\text{min}$ ) was started following the establishment of pneumoperitoneum, as mean arterial pressure was rising. All increases in mean arterial pressure >20% above baseline values were corrected within 1 min by increasing the infusion rate of remifentanil by 50%. As a consequence, only mild increase in mean arterial pressure was recorded during pneumoperitoneum and did not change significantly during tumor manipulation. Intraoperatively, the use of 0.25 mg of b-blocker was necessary in one of nine patients and a rescue dose of sodium nitroprusside in another one who had a history of myocardial infarction. The remaining patients did not require b-blockers as they were premedicated with b-blockers as part of the preoperative antihypertensive treatment and complemented by the high dose of remifentanil which reduces heart rate. No patient presented cardiac arrhythmias. Neither vasoconstrictive nor inotropic drugs were needed immediately after adrenalectomy, as the remifentanil infusion decreased and colloid solution were infused. One patient had experience of bradycardia, <45 bpm, which was controlled by 0.6 mg of atropine.

After tumor removal, the infusion rate of remifentanyl was diminished and all patients received 0.15 mg/kg IV morphine to achieve adequate postoperative analgesia. At the end of the operation, residual neuromuscular blockade was reversed with neostigmine and atropine. At skin closure, sevoflurane and N<sub>2</sub>O were discontinued simultaneously, and remifentanyl infusion was decreased in increments of 50% until it was discontinued when the surgical dressing was applied. The median consumption of remifentanyl per patient throughout the study was 2.3 mg (2.1-5.4 mg).

In the recovery room, mean arterial pressure was higher than 65 mmHg in all patients. Three patients required metoclopramide administration because of nausea. Three patients experienced postoperative nausea and vomiting in spite of the pretreatment with ondansetron. Pain in the immediate postoperative period was mild to moderate. Mean consumption of morphine during the first two hours was  $6 \pm 3.5$  mg and ranged from 4 to 12 mg. None of the patients complained of awareness during anesthesia.

## Discussion

In this prospective case-series study, we preferred a balanced anesthetic scheme of sevoflurane in nitrous oxide supplemented with remifentanyl and sustained neuromuscular block. Laparoscopic adrenalectomy to treat pheochromocytoma results in marked catecholamine release during pneumoperitoneum and tumor manipulation. This study documents that laparoscopic adrenalectomy for pheochromocytoma results in easy control of hemodynamic changes using a continuous infusion of remifentanyl. Hypotension after tumor removal (defined as a SBP <85% of baseline value or an absolute value of <90 mmHg) was treated with additional colloids fluids and decreasing the remifentanyl infusion rate by 25-50%.

Remifentanyl is a highly potent opioid with a rapid onset and a short duration of action due to its rapid hydrolysis by esterases in blood and tissues. The pharmacokinetics of remifentanyl is consistent with its rapid

elimination by blood and tissue esterases. The rapid onset and short duration of action of remifentanil make it well suited for continuous infusion and titration of dose (infusion rate) to the desired degree of effect<sup>8</sup>. When added to sevoflurane, remifentanil is as effective and safe<sup>9</sup>. The pharmacokinetic and pharmacodynamic properties of remifentanil, as well as its propensity not to accumulate in human tissues, could make it advantageous for surgical anesthesia in procedures of intermediate and long duration, like laparoscopic adrenalectomy to treat pheochromocytoma.

In the present study remifentanil infusion was adjusted to maintain systolic arterial pressure between 120-170 mmHg. Increased infusion rate of remifentanil was used (up to 3 µg/kg/min in two patients) to prevent and treat marked hemodynamic changes from catecholamine release during tumor manipulation.

Balanced anesthetic scheme of volatile and opioids were preferred by other investigators using supplement of vasodilator and a b-blocker or calcium channel blockade as alternative<sup>9,10,11</sup>. There is ample evidence that sodium nitroprusside (SNP) has been successfully used, and may be effective in causing arterial dilatation and suppressing the hypertensive response to circulating catecholamines<sup>12</sup>. SNP was specifically advocated to supplement the anesthetic management. In the present study, however, remifentanil, as itself is a potent sympatholytic agent, reduced the need for sodium nitroprusside and b-blocker as it induced vasodilation and diminished heart rate.

A combination of intravenous opioid as remifentanil and inhaled drugs maintain hemodynamic stability during the intraoperative period. In our study, the hemodynamic changes were managed by titrating remifentanil to desired effect according to the needs, with a rapid emergence from anesthesia, thus avoiding persistent sympatholysis after tumor removal. Our patients were pretreated with phenoxybenzamine, a persistent  $\alpha$ -adrenoceptor blockade, so patient received an average of 100 ml colloid solution to maintain central venous pressure at least 8 mmHg. Thus, in all patients mean arterial pressure was higher than 65 mmHg in postoperative period and none patient developed cardiopulmonary

complications.

In conclusion, patients with pheochromocytoma should ideally be managed by an experienced team of endocrinologists, endocrine surgeons and anesthetists. When the patient's condition is recognized and treated pharmacologically to responses to catecholamine release, a balanced anesthesia in combination of remifentanil infusion with inhaled agent, should be able to control acute hemodynamic changes that occur during laparoscopic adrenalectomy for pheochromocytoma.

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