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Research Article

Clevidipine as a Means of Controlling Hypertension in Laparoscopic Surgery

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Abstract

Introduction: Hypertension is one of the most prevalent diseases in the developed world. In the perioperative setting, hypertensive patients are particularly susceptible to haemodynamic changes during anaesthesia. Ensuring adequate control of Arterial Pressure (AP) is especially important during laparoscopic surgery because of the severe haemodynamic effect caused by the pneumoperitoneumthat is provoked. Numerous antihypertensive drugs have been proposed for this purpose. One that has been recently approved for the rapid reduction of AP in the perioperative setting is clevidipine,a new, ultrashort-acting, calcium antagonist. To date, no studies have been published on the usefulness of this drug for AP control during laparoscopic surgery.

Materials and Method: We present a series of five cases of laparoscopic surgery in which, after normal analgesia, optimal AP control was not achieved and so clevidipine was used as a hypotensive agent.

Results: In all five cases, the AP was controlled quickly and without side effects. Implementation was simple and did not require invasive monitoring.

Conclusions: We believe clevidipine is a useful drug for controlling hypertension during laparoscopic surgery. Further, more extensive, studies are required to validate this indication.

Keywords: Clevidipine; Hypertension; Laparoscopic surgery

Introduction

Hypertension (HTN) is one of the most prevalent diseases in the developed world. It is estimated to affect one billion people worldwide [1]. The overriding impact of this condition is its very high associated mortality. Hypertension is associated with half of all deaths from heart disease and stroke, and it is usually considered to form part of metabolic syndrome.

For the anaesthesiologist, the intraoperative management of patients with HTN poses a challenge due to their greater sensitivity during this period. This increased risk of intraoperative HTN is exacerbated in certain treatments, such as laparoscopic surgery, during pneumoperitoneum, due to the hypertensive effect of the CO_2 and the release of cortisol and catecholamines, especially noradrenaline.

In these patients, haemodynamic changes may be exacerbated by alterations to self-regulatory mechanisms, which often require the use of hypotensive drugs.

The haemodynamic instability that often arises during the intraoperative phase, due to surgical or anaesthetic causes, is exacerbated in patients with HTN. In this situation, under time pressure, the clinician must choose whether to adopt a permissive or a strict attitude to haemodynamic monitoring [2].

This haemodynamic lability is not innocuous, it can overload homeostasis and lead to increased morbidity and mortality in the medium and long term [3]. In the short term, this instability has been associated with myocardial ischaemia, bleeding from the surgical bed and stroke (haemorrhagic or ischaemic) [3,4]. In the medium term, it also increases mortality arising from kidney failure, stroke and systolic dysfunction.

In laparoscopic surgery, maintaining haemodynamic monitoring of the patient is often highly challenging, especially when the HTN is poorly controlled. Although the haemodynamic impact of pneumoperitoneum has been extensively studied, some of its effects remain poorly understood.

It is well established that laparoscopic procedures, due to CO_2 insufflation, bloating, chest compression and the Trendelenburg position, difficults venous return, increase peripheral vascular resistance and mean arterial pressure and stimulate the release of catecholamines.

The initiation of pneumoperitoneum triggers an adrenergic response, provoking a significant increase in mean AP, a change in the heart rate (opinions differ as to whether this increases [5], decreases [6-8], or remains unchanged [9-12]) and increased peripheral and pulmonary vascular resistance [6].

Numerous studies of catecholamine release have recorded increased levels of noradrenalin in the vascular territories, unrelated to adrenaline levels. Increases in other stress hormones, such as cortisol, have also been measured [13]. This change produces a presser response, with an increased afterload that is directly related to the establishment of pneumoperitoneum [14]. Some studies have even considered the use of drugs such as dexmedetomidine, a highly

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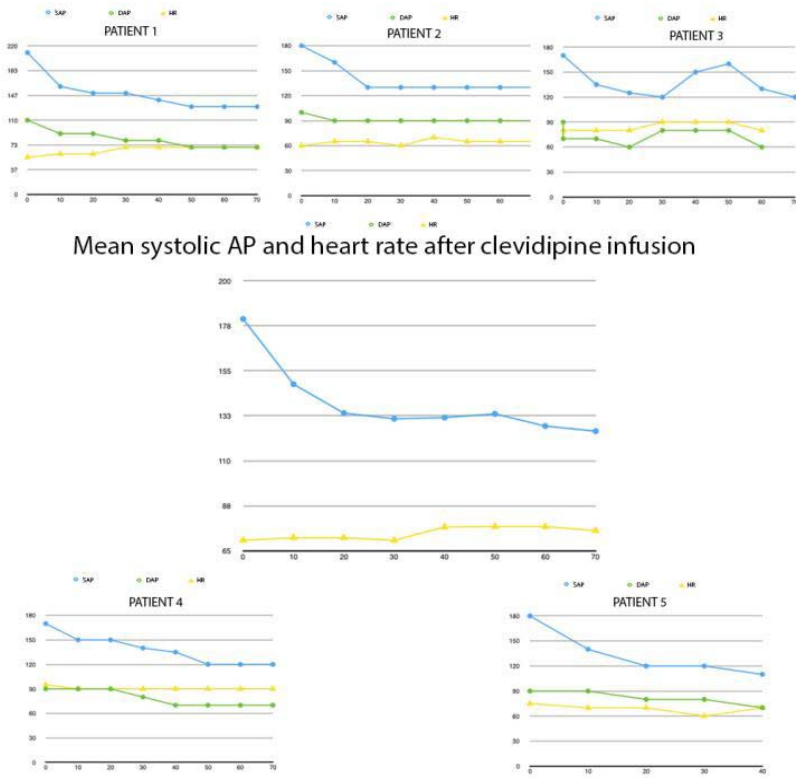

Figure 1: The evolution of AP values.

selective agonist of the alpha-2 receptor, or esmolol, a cardioselective beta-1 receptor antagonist, in order to reduce the adrenergic response to pneumoperitoneum [15].

Moreover, the very action of CO_2 has also been postulated as one of the causes of these haemodynamic changes, compared with surgical approaches in which the abdominal wall is lifted with another type of gas, such as helium or nitrous oxide, or even without the intervention of gas, by lifting the abdominal wall using other devices (e.g., Laparolift®).

Severe haemodynamic changes are said to occur at >30% above normal levels, although slight hypercapnia can produce manifestations of sympathetic overstimulation, such as tachycardia or increased afterload. Severe hypercapnia can lead to a reduction in the left ventricular function and a negative isotope effect [16].

In the comparative study by Andersson et al. [12], significant differences were found between the Laparolift device and conventional laparoscopy; the latter produced a greater increase in mean arterial pressure, central venous pressure, systemic vascular resistance, peak airway pressure and $PaCO_2$.

The anesthesiologist must preserve the homeostasis of the patient, and in situations of HTN the administration of an antihypertensive treatment may be indicated, once an adequate depth of anaesthesia and analgesia has been assured.

In anesthesia, the ideal antihypertensive would be a drug that after intravenous administration has a pharmacokinetic profile that fits as closely as possible to changes in the surgical aggression; moreover, it should be predictable regardless of patient characteristics, easy to prepare, dose adjustable and have little impact on other haemodynamic parameters.

Many antihypertensive agents are available, including nitroglycerine, sodium nitroprusside, labetalol, esmolol, hydralazine, fenoldopam, urapidil and nicardipine [17]. Each has a different pharmokinetic profile and while they are all useful in intraoperative management, they also present limitations. Thus, nitroglycerine can aggravate HTN with the concomitant use of phosphodiesterase inhibitors; sodium nitroprusside requires caution in situations of aortic coarctation; labetalol can worsen situations of heart failure, bradycardia, second or third-degree heart block, chronic obstructive pulmonary disease or asthma; esmolol presents similar limitations with respect to conduction and respiratory disorders; hydralazine is contraindicated for patients with ischaemic heart disease or aortic dissection; fenoldopam should be used with caution in patients with glaucoma and the concomitant use of beta-blockers; urapidil is not recommended for patients with aortic stenosis; and nicardipine should not be used in situations of heart failure or marked aortic stenosis. Therefore, for each patient the most appropriate antihypertensive must be selected. Some of them require dilutions and dosages, of varying degrees of complexity, or may present toxicity.

The Food and Drug Administration, recently, and subsequentlythe Spanish Medicines Agency have approved a new antihypertensive drug, clevidipine, for use in the perioperative context [18].

This recent approval of clevidipine for the intraoperative treatment of HTN expands our therapeutic arsenal. This drug presents

the following advantages. Its pharmacokinetic characteristics are well suited to the intraoperative haemodynamic instability of hypertensive patients. Its commercial form is easy to use and prevents errors in preparation and dosing, and in most patients it enables a smooth transition to oral administration.

This drug is an intravenous dihydropyridine calcium antagonist, which is ultrashort-acting and provides easy titration, with a dose-dependent effect. Its metabolism depends on plasma and extracellular esterases, which give it a mean duration in the blood of 15 minutes. It is not dependent on kidney or liver function. Primarily, it acts on the arterial smooth muscle, on the L-type calcium channels, thus decreasing peripheral vascular resistance and mean arterial pressure, without causing alterations in the venous system, and stabilises cardiac output, pulse and preload [19-21].

Many clinical trials have shown that clevidipine effectively reduces blood pressure safely and predictably, regardless of patient characteristics, and that it does not require invasive monitoring. Moreover, it facilitates a smooth transition to oral treatment with other calcium channel antagonists, beta-blockers or ACE inhibitors.

In general, this calcium antagonist for intravenous application, which is ultrashort-acting (unlike nicardipine), independent of age, weight and kidney-liver function, and which does not require dilution or dose adjustment, comes very close to the specifications for an ideal hypertensive drug in intraoperative anesthesia management.

Clevidipine has been tested in healthy volunteers [20], hypertensive patients [19] and hypertensive patients undergoing cardiac surgery. In all cases, satisfactory results have been obtained and the drug has been approved for clinical use [4]. Thus, Ericsson conducted a phase I trial to test its safety and tolerability in healthy volunteers, and Schvieller studied the drug's pharmacokinetics in patients with mild to moderate HTN [19]. The ESCAPE 1 and 2 studies have validated its use in the perioperative management of cardiac surgery. The ECLIPSE study compared the efficacy and safety of clevidipine with that of the antihypertensive drugs most frequently used in cardiac surgery for the management of acute HTN (nitroglycerine, nitroprusside and nicardipine), and concluded that it provides better control than the first two and a similar degree of effectiveness to nicardipine, with no significant differences in mortality or adverse effects during the first 30 days after surgery [2,22].

The aim of the VELOCITY study was to evaluate the efficacy and safety of clevidipine in the management of severe hypertensive crises in emergency and intensive care departments. It was found to be effective, providing fast and safe control of AP. It also achieved a high success rate in the transition to antihypertensive oral therapy [23].

The ACCELERATE trial tested the ability of clevidipine to normalise systolic AP in patients with intracranial haemorrhage and HTN, and reported that normal AP was achieved in an average of five minutes [24].

The effective use of clevidipine in intraoperative management has also been reported in certain clinical situations, such as pheochromocytoma surgery [25,26], spinal surgery for adolescent patients, and surgery for paediatric patients. However, this conclusion has not been validated by controlled clinical trials [27-29].

Mild adverse effects of clevidipine that have been reported include nausea, headache, chest pain and thrombophlebitis, as well as a possible increase in heart rate or a negative isotropic effect in patients with heart failure. In addition, there may be a rebound effect with HTN and tachycardia on the cessation of treatment after prolonged infusions. Studies have also found adverse effects such as an increased incidence of acute renal failure (ESCAPE-1) and an increased incidence of atrial fibrillation (ESCAPE-2), although with no significant differences with respect to other anti hypertensives [4].

Clevidipine also presents some limitations regarding possible allergies to the excipients employed or the need for it to be stored in a refrigerator.

Clevidipine has also been associated, experimentally, with a decreased minimum alveolar concentration of isoflurane [30].

Materials and Method

We describe a clinical series of five patients with a history of HTN, controlled with medical treatment and proposed for scheduled laparoscopic surgery, ASA II. Allpresented intraoperative HTN, which was treated with clevidipine by intravenous infusion.

The characteristics of the patients and the surgical technique are described in (Table 1).

All anaesthesia was performed by expert anesthesiologists, with more than 15 years' experience, following the usual method for this surgery at our hospital.

The monitoring procedure was standard, based on noninvasive blood pressure, ECG, SpO_2, capnography, levels of halogenated gases and neuromuscular relaxation, and controlling anesthetic depth by reference to the bispectral index.

A balanced anaesthetic technique was performed by induction with propofol 2 mg/kg, fentanyl 2 mcg/kg and rocuronium 0.6 mg/kg and maintained with sevoflurane, adjusting the opioid supply according to clinical judgment in order to obtain adequate analgesia.On the completion of pneumoperitoneum, all five patients experienced a progressive elevation of AP levels, which persisted despite the adequate analgesia and anesthetic depth achieved, in the clinician's opinion.

The administration of clevidipine was then indicated as an antihypertensive treatment.

Clevidipine is supplied in a lipid formulation derived from soy and egg, similar to propofol, at a concentration of 0.5 mg/ml. Its titration is straightforward; the infusion is initiated at 1-2 mg (2-4 ml/h) [31] and the dose may be increased every 90 seconds. As the pressure values approach the level required, the increase should be more gradual, every 5-10 minutes. The maintenance dose to maintain good control of AP, in most patients, is 4-6 mg/h, although in severe hypertensive crises, up to 32 mg/h has been used.

In our study, the initial dose administered was 2 mg/h, which was progressively increased every 5 minutes, adjusted according to the AP observed, to achieve adequate control, taken as equivalent to pre-induction values (10% change from baseline).

Table 1: The characteristics of the patients and the surgical technique.

	Sex	Age (years)	Clinical history	Type of surgery
Patient 1	Male	63	Intermittent claudication, hypercholesterolaemia	Laparoscopic pyelotomy
Patient 2	Male	78	Hypertension, ischaemic heart disease, hyperlipidaemia. ex-smoker, ex-drinker	Laparoscopic cholecystectomy
Patient 3	Female	71	HTN, dyslipidaemia	Hysterectomy + double adnexectomy + laparoscopic omentoplasty
Patient 4	Male	45	HTN, DM-II, dyslipidaemia, morbid obesity	Bariatric surgery, gastric bypass
Patient 5	Male	74	Double hereditary haemochromatosis, hepatic steatosis	Laparoscopic cholecystectomy

Table 2: The average infusion time was 61.46 minutes, and normal AP values.

	Total dose administered (mg)	Infusion time (min)	Time needed to achieve control of AP (min)
Patient 1	14	105	5
Patient 2	1.5	30	5
Patient 3	4.25	120+90*	10-May
Patient 4	5	90	15
Patient 5	11	90	10

Results

The present study adhered at all times to the provisions of the Declaration of Helsinki and Spanish legislation on patient rights (Act No. 15/2002). No clinical data other than those described above were collected.

The evolution of AP values is shown in (Figure 1), together with the average values for all patients. In all cases, adequate AP control was achieved, in an average time of 7.05 minutes, with the administration of an average dose of 8.27 mg (maximum 14 mg, minimum 1.5 mg). The average infusion time was 61.46 minutes, and normal AP values were maintained at all times (Table 2).

Discussion

In our context, laparoscopic surgery is commonly required and it is sometimes very challenging to treat HTN, especially in patients who have this as an underlying condition. In response, clinicians often seek to deepen the anaesthesia and increase the analgesia, but fail to achieve satisfactory results because this method does not address the pathophysiological mechanisms that have provoked the HTN crisis.

In the present study, clevidipine was used for the treatment of HTN in a series of patients with baseline HTN who had suffered a hypertensive crisis in the intraoperative phase as a result of pneumoperitoneum, despite (in the opinion of an expert anaesthesiologist) receiving an adequate level of analgesia and anaesthetic depth.

A rapid decrease in AP was achieved rapidly (starting in the first five minutes and fully achieved in 15 minutes) but gradually, with the dose being adjusted in a linear fashion. Thus, the clevidipine treatment successfully lowered AP to normal (similar to preoperative) levels. AP was controlled throughout the process, and the dose was adjusted to surgical aggression at all times. There was no rebound HTN after the infusion was suspended, or adverse side effects or variations in heart rate. The anaesthesiologists responsible for each case found the drug to be straightforward and effective in use. Invasive monitoring was not required.

In conclusion, we find that pneumoperitoneum causes abrupt haemodynamic changes, related especially to the patient's position, the insufflation of CO_2 and the release of catecholamines.

Laparoscopic surgery is now common and it is being applied in a growing range of procedures. We believe that clevidipine may present optimum pharmacokinetic and pharmacodynamic features for the control of HTN in laparoscopic surgery. To the best of our knowledge, no previous research has been published on the antihypertensive use of clevidipine in this indication. Its use in these circumstances may be appropriate, and in this belief we evaluated a number of clinical cases in which it was used.

Conclusion

Clevidipine is a calcium channel blocker that has been approved for the treatment of hypertension in the perioperative setting. It has a suitable pharmacokinetic and pharmacodynamic profile, and is easy to use, regarding both its presentation and its dosage. It has predictable effects, regardless of the patient's age, weight and kidney-liverfunction. Clinical trials have shown it to be safe, with few side effects. To date, it has mainly been used in cardiac surgery, and further experience is needed in other types of interventions. We used it in the treatment of hypertension related to pneumoperitoneum in laparoscopic surgery, and achieved excellent results with no side effects. The drug's pharmacokinetic profile was found to adapt well to the hemodynamic fluctuations presented by these patients.

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