Perioperative Use of Clevidipine: A Systematic Review and Meta-Analysis

Angel Espinosa1*, Javier Ripollés-Melchor2, Rubén Casans-Francés3, Alfredo Abad-Gurumeta4, Sergio D. Bergese5, Alix Zuleta-Alarcon5, Francisco López-Timoneda6, José María Calvo-Vecino2*, Evidence Anesthesia Review Group¶

1 Center of vascular and thoracic surgery and intensive care, Örebro University Hospital, Örebro, Sweden, 2 Department of Anesthesia, Complutense University of Madrid, Infanta Leonor University Hospital, Madrid, Spain, 3 Department of Anesthesia, University of Zaragoza, Lozano Blesa University Hospital Clinic, Zaragoza, Spain, 4 Department of Anesthesia, La Paz University Hospital, Madrid, Spain, 5 Departments of Anesthesiology and Neurological Surgery, The Ohio State University, Columbus, Ohio, United States of America, 6 Department of Anesthesia, Complutense University of Madrid, San Carlos University Hospital, Madrid, Spain

¶ Complete membership of the Evidence Anesthesia Review Group is provided in the Acknowledgments.

* angel.espinosa@regionorebrolan.se; drangelespinosa@gmail.com (AE); jmaria.calvo@salud.madrid.org (JMCV)

Abstract

Background
Clevidipine is an ultrashort-acting drug for rapid reduction of blood pressure by selectively acting on the L-type Ca2+ channels on arteriolar smooth muscle. The drug’s ultrashort action in reducing the blood pressure is due to its rapid hydrolysis by blood and extravascular tissue esterases, which does not depend on hepato-renal metabolism and excretion. An analysis of the perioperative management of blood pressure should be considered to compare with other intravenous antihypertensive agents.

Methods
Analyses of the available evidence in randomized clinical trials following the PRISMA methodology as well as clinical significance according to the GRADE system were conducted. Placebo versus other antihypertensive drugs studies were included. Statistical assessments were done using the X2 and I2 tests.

Results
Clevidipine was more effective in maintaining the blood pressure within pre-specified ranges compared with other antihypertensive drugs (MD, -17.87 CI 95%: -29.02 to -6.72; p = 0.02). The use of Clevidipine versus placebo and rescue antihypertensive intravenous drug showed a clear reduction in rates of treatment failure (RR 0.10; IC 95%; 0.05–0.18; p <0.0001). There was no difference in the incidence of adverse events compared with placebo (RR 1.47; 95% CI 0.89 to 2.43, p = 0.14) and with other antihypertensive drugs (RR 0.78, 95% CI 0.45 to 1.35; p = 0.37). In addition, there was no difference in the incidence of
atrial fibrillation (AF) between clevidipine and control groups (RR 1.09, IC del 95%: 0.65 a 1.83; p = 0.73).

Conclusions

Clevidipine is an ultrafast-acting drug that is highly effective for management of perioperative arterial hypertension. It is devoid of adverse effects associated with the use of other IV antihypertensives. Its favorable pharmacodynamic and pharmacokinetic properties make clevidipine the drug of choice for the management of acute perioperative hypertension. It is important to emphasize the need for further studies with a larger number of patients to confirm these findings and increase the degree of evidence.

Introduction

Multiple intravenous medications are currently used to control blood pressure (BP) in the perioperative period, and all these drugs have advantages and disadvantages [1, 2].

Perioperative Blood Pressure (BP) in hypertensive patients has been associated with a worse outcome, hence, many treatment protocols require invasive BP monitoring during high-risk procedures [3]. Acute perioperative hypertension (HTA) affects up to 80% of patients undergoing cardiac surgeries and over 25% of patients undergoing major non-cardiac procedures [4].

Pre-existing hypertension (affecting more than two-thirds of cardio surgical patients) contributes to development of acute perioperative hypertension and often is a common reason for postponing surgery [5, 6].

Other ultrafast-acting drugs such as nitroglycerin or nitroprusside have the disadvantage of producing intense venodilation, which may decrease the preload and impair pulmonary circulation. These effects can offset the benefits of rapid BP control.

Others drugs like dihydralazine are effective in lowering BP by intravenous bolus but have a residual effect that can last for hours. Labetalol can generate undesired cardiovascular effects that will narrow its clinical utility. Urapidil is a commonly used perioperative drug with a dual mechanism of action: α1-adrenoceptor antagonism, 5-HT1A receptor agonism, and possible central α2-adrenoceptor agonism. Its use has been associated with postsurgical hypotension after 1 hour of continuous infusion [7].

Clevidipine Butyrate acts on L-type Ca2+ channels that regulate the Ca2+ flow in arteriolar smooth muscle cells during depolarization. By relaxing the arteriolar smooth muscle, it reduces peripheral vascular resistance, increases cardiac output and reduces blood pressure. Clevidipine has no effect on capacitance vessels and the venous tone, and it does not produce undesirable changes in afterload, including the left ventricle filling pressure and left ventricular peak pressure [8]. Clevidipine is a dihydropyridine just as nicardipine and nifedipine, which are considered first-line drugs for hypertensive emergencies owing to their strong vasodilatory effects and low propensity to cause abnormalities in cardiac conduction and contractility [9–11].

Several studies have shown clevidipine’s potential in blood pressure maintenance. A study published in in 2007 showed that preoperative clevidipine administration was effective in decreasing blood pressure and achieving a 92.5% rate of treatment success with a failure of 7.5% when compared with placebo (82.7%, 43 of 52; P < 0.0001). The authors agreed that a “modest” increase in heart rate from baseline values was reported for the clevidipine group. However the study considers 105 patients for randomization with only 53 patients receiving clevidipine and 52 placebo.[12] One year later, in 2008, Singla et al. reported similar treatment
success rate (91.8%) when Clevidipine was administrated in post operatory setting. The study analyzed data collected from only 69 patients dosed with study drug and 49 placebo recipients. [13] The ECLIPSE study results—published in 2008—showed no difference in the incidence of myocardial infarction, stroke or renal dysfunction for patients treated with Clevidipine when compared with other antihypertensive drugs (nitroglycerin, sodium nitroprusside, and nicardipine).[14] This is an open label, perioperative study design, reporting outcome from 752 patients receiving clevidipine compared with 756 patients receiving different comparator drugs.[14]

The existing published data analyzed results obtained from studies investigating the outcome of clevidipine administration at different time points during perioperative intervention. Our study offers an integrated analysis of clevidipine administration during the pre-operative, intraoperative, and post-operative period.

In an attempt to assess the effectiveness of clevidipine as an optimal agent for perioperative blood pressure management, we analyzed the accumulated evidence of the intraoperative use of clevidipine in adults and compared its safety and efficacy on blood pressure management relative to other existing hypotensive drugs used during anesthesia.

**Material and Methods**

**Study design**

Systematic review according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statements [15]. The Cochrane Handbook for Systematic Reviews of Interventions [16] and Jakobsen et al. "8 steps methodological recommendations" [17].

The absence of sufficient data in studies prevented the protocol to be included in the PROSPERO registration, although P-PRISMA agreement has been faithfully followed (S1 PRISMA Checklist) [18].

**Inclusion criteria**

PRISMA [15] methodology was used for selecting studies, based on the following criteria:

1. Participants: Adult patients scheduled for surgery in which Clevidipine was administered to control blood pressure in the perioperative period.
2. Type of Intervention: Administration Clevidipine at any dose.
3. Type of comparison: placebo or other antihypertensive drugs.
4. Types of studies: Randomized clinical trial (RCT) in which the effectiveness of antihypertensive therapy and/or complications associated with treatment and adverse effects associated with the drug are reported and analyzed. Those presented as posters or conference papers were excluded.

**Source of information**

Different search strategies (last updated in January 2015) were established to identify relevant studies containing the inclusion criteria, using EMBASE, MEDLINE, and the Cochrane Library.

**Search items**

Keywords such as “Clevidipine” and “randomized control trial” were used. Studies were restricted to adult human subjects. There was no restriction on date or language. RCTs with
complete published data only were included. There was no limited period of time in the literature search.

Study selection and data extraction
Two independent researchers assessed each title and abstract, to rule out any irrelevant RCT, and identify potentially relevant ones. Those who met the inclusion criteria described above were selected. The data extraction was performed by two different researchers, and a third investigator was required to answer any discrepancy by analyzing more in depth. The authors reviewed data analysis during the transcription process to avoid errors.

Item data
PICOS characteristics (patient, intervention, comparison, outcome and design) of the included studies were collected.

On the other hand, data on the frequency, type of complications, and adverse events of related drugs were collected.

We used the PICO system to set the research question, with a universe of Patients including adults from 18 years old and older, Intervention being the use of an infusion of an antihypertensive medication with a Comparison of Clevidipine vs. placebo plus rescue antihypertensive intravenous drug or a control drug, and the Outcome the safety and efficacy of the blood pressure control between pre-established limits.

The question was formulated as n°1 – in patients with perioperative hypertension, is Clevidipine either more effective or safe for maintaining the blood pressure in a specific range than other antihypertensive drugs? And n°2 – in patients with perioperative hypertension, is Clevidipine either more effective or safe for maintaining the blood pressure in a specific range than placebo plus rescue antihypertensive intravenous drug?

Bias assessment of the included studies
Cochrane test for assessment of possible bias was implemented [16]. We used seven domains of this test to evaluate the quality of methodologies of the studies included in the analysis. If one or more domains were determined to be high risk, we classified the RCT as having a high risk of bias. If the test cannot produce final results, the RCT was also classified as having a high risk for bias [16].

Outcome endpoints
Effectiveness of Clevidipine vs. Placebo plus rescue antihypertensive intravenous drug. The incidence of treatment failure was defined as the inability to lower systolic blood pressure below 15% of the baseline or premature and permanent interruption of the trial treatment for any reason within 30 minutes after the onset of the drug. Alternative antihypertensive treatment could be instituted as per institutional practice after treatment failure.

Effectiveness of Clevidipine vs. other antihypertensive drugs. Evaluation using the analysis of the area under the curve (AUC) of the excursions of the blood pressure (BP) beyond the upper and lower limits defaults, normalized per hour (AUCSBP—D), or defined as the total area off the curve of time, mean arterial pressure (i.e. both above and below the clinical range predefined as a target), and normalized by time (AUCMAP—D, in units of mmHg : min−1).

Clevidipine safety compared to placebo plus rescue antihypertensive intravenous drug and to other antihypertensive drugs. The incidence of reported serious adverse events (as defined by the authors), including atrial fibrillation. Drug-related adverse events defined as the
incidence of adverse events (AEs) since the beginning of the study drug and evaluated by a physi-cian regardless of the relationship with Clevidipine.

**Statistical analysis**

Review manager ("Revman 5.2.3") [19] for MAC (Cochrane collaboration, Oxford, UK) and OpenMetanalyst [20] were used.

To measure the effect of dichotomous and continuous variables, risk ratio (RR) and mean difference was used respectively, both having a 95% confidence interval.

The model of Mantel-Haenszel for random effects was used as statistical method of the meta-analysis for the dichotomous variables, and inverse variance for continuous variables [21]; the results were presented as relative risk (RR) with 95% confidence interval.

Forest plot was built considering $p < 0.05$ as statistically significant effect. Statistical heterogeneity was assessed using the I² statistic [22]; I² less than 25 percent was defined as low heterogeneity; between 25 and 50 percent, moderate heterogeneity; greater than 50 percent, high heterogeneity. One $\chi^2$ test was conducted for heterogeneity, considering $p$ value of $< 0.10$ as statistically significant.

When statistical heterogeneity was found, results of the meta-analysis were presented using a random effects model. When no statistical heterogeneity was found, the results were pre-sented as fixed effects model. "Funnel plot" technique was used for the analysis of publication bias, only if at least ten clinical trials were included in the meta-analysis [16].

**Level of evidence and clinical significance**

The GRADE [23] methodology was used to evaluate the quality of the evidence (www.gradeworkinggroup.org) of our findings. A thorough assessment of the balance between beneficial and harmful effects of Clevidipine was performed to evaluate the clinical significance of the effects of the intervention [24].

**Results**

**Studies selection**

Of the 160 references found in databases, 17 were fully analyzed, and finally, 4 were included for systematic review and meta-analysis (See Fig 1). Two independent reviewers analyzed the risk of bias in Cochrane tool [16]. Any disparity was resolved by involving a third reviewer. Methodological quality was presented in a summary table (Fig 2). RCTs that evaluated the use of Clevidipine versus placebo plus rescue antihypertensive intravenous drug or versus other antihypertensive drugs were selected to be included in the analysis. The results are presented in Tables 1, 2 and 3. (In addition, 1 article was not included in the analysis, due to inconsistencies on efficacy, although it is considered important and is shown on the table).

**Primary results**

Efficacy of Clevidipine vs Placebo plus rescue antihypertensive intravenous drug. The use of Clevidipine vs placebo, significantly decreased the failure in treatment (RR 0.10; IC 95%; 0.05–0.18; $p < 0.0001$) (Fig 3).

Efficacy of Clevidipine vs other antihypertensive drugs. AUC SBP-D: Median AUC SBP-D was significantly lower in patients treated with Clevidipine than in patients treated with other antihypertensives (MD, -17.87 CI 95%: -29.02 to -6.72; $p = 0.02$) (Fig 4).

Safety. Differences in the incidence of adverse events between Clevidipine and placebo and rescue antihypertensive intravenous drug groups (RR 1.47; 95% CI 0.89 to 2.43, $p = 0.14$),
in the comparison with other antihypertensive drugs (RR 0.78, 95% CI 0.45 to 1.35; p = 0.37) or when analyzed together (RR 1.05; 95% CI: 0.63 to 1.77; p = 0.06) were not found (Fig 5).

**Atrial fibrillation.** No differences were found in the incidence of AF between clevidipine and control groups (RR 1.09, IC del 95%; 0.65 a 1.83; p = 0.73) (Fig 6).

**Publication bias**

The insufficient number of RCTs included prevented the assessment of publication bias using the Funnel plot technique [16]. (Fig 2).

**Level of evidence (Fig 7)**

**Discussion**

To our knowledge, this is the first meta-analysis of the literature available for clevidipine. An optimal agent for perioperative blood pressure management should be a specific arterial
vasodilator with rapid onset, short-term duration of effect, having low toxicity, and without the potential of causing reflex tachycardia [25].

Most vasodilators, such as nitroglycerin and sodium nitroprusside, act on both arterioles and venules and may cause undesirable reduction in cardiac preload. In addition, these drugs may impair renal and cerebral perfusion and induce intracranial hypertension. Nitroglycerine has an onset of effect of 2 to 5 minutes and duration of effect up to 20 minutes. Its administration is commonly associated with reflex tachycardia. Nitroprusside acts as arterial and venous dilator that can cause marked hypotension and can lead to cyanide toxicity [26, 27].

Beta-blockers, such as esmolol, decrease blood pressure, heart rate, and cardiac output and, therefore, they should be avoided in patients with bradycardia [28]. With labetalol, a selective alpha 1 and non-selective beta-blocker, cardiac output is maintained, and heart rate is modestly decreased or maintained. Labetalol has a rapid onset of action (2–5 minutes) and duration of action of 2–4 hours [6, 28].

Clevidipine has a rapid onset and duration of action, which allows its classification as an ultrashort-acting agent. The drug is manufactured as an emulsion of soybean oil and purified...
egg yolk phospholipids that make it lipophilic, with water solubility of 0.1 mg/ml [6, 29]. The intravenous product is a mixture of two enantiomers S- and R-clevidipine [30]; each enantiomer has equipotent antihypertensive activity. At body temperature, the drug binds to plasma proteins (~99.7%) [31]. It is metabolized to inactive compounds by plasma and tissue esterases, with a mean depuration ratio of 0.121 Lit.min⁻¹kg⁻¹ [32] and a volume of distribution in steady-state of 0.6 L kg⁻¹ [33]. Pharmacokinetic studies have shown a linear relationship between dosage and arterial blood concentration, achieving a steady state 2 minutes after the start of the intravenous perfusion [34]. Clevidipine does not depend on renal or hepatic function for its metabolism, and therefore, it has a superior safety profile compared to nicardipine (hepatic metabolism) and nimodipine (oxidative demethylation and dehydrogenation). Unlike the latter drugs, clevidipine can be safely used in patients with hepatic and renal disease. Clevidipine has been mostly studied in patients undergoing various surgeries, mostly cardiac procedures and to our knowledge clinical trials in neurosurgical patients have not yet been published [35].

Clevidipine reduces peripheral vascular resistance and, therefore, increases stroke volume and cardiac output. Its capability to selectively reduce the afterload prevents the influence over other hemodynamic parameters (increase left ventricle filling pressure and pulmonary wedge pressure) [8]. Its administration decreases systolic BP within the first 2–4 minutes after infusion [12], and baseline systolic BP and heart rate are achieved 15 minutes after the infusion is discontinued [36]. In contrast, nicardipine’s longer half-life results in a prolonged post-

| Table 1. PICO Characteristics of Included Studies. |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Study | Year | Patients | N | Intervention | Comparison | Outcomes | Design | Country | Financed |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Powroznyk et al. | 2003 | CABG intervened adult patients | 39 | Clevidipine 0.3mcg/kg/min | Nitroprusside 0.5mcg/kg/min | Blood pressure control. Hemodynamic parameters | Multicenter randomized clinical trial | UK | AstraZeneca R&D Môndal, Sweden |
| Levy et al. (ESCAPE-1) | 2007 | Cardiac surgery intervened adult patients | 105 | Clevidipine 0.4–8 mcg/kg/min | Placebo (rescue: Antihypertensive drug not specified) | Antihypertensive efficacy (Decrease in SBP >15% of baseline) during the first 30 minutes | Placebo-controlled multicenter randomized clinical trial | USA | The Medicines Company |
| Singla et al. (ESCAPE-2) | 2008 | Cardiac surgery intervened adult patients | 110 | Clevidipine 0.4–8 mcg/kg/min | Placebo (rescue: Antihypertensive drug not specified) | Antihypertensive efficacy (Decrease in SBP >15% of baseline) during the first 30 minutes | Placebo-controlled multicenter randomized clinical trial | USA | The Medicines Company |
| Aronson et al. (ECLIPSE) | 2008 | Cardiac surgery intervened adult patients | 1507 | Clevidipine 0.3–8 mcg/kg/min | Nitroprusside, nitroglycerine or nicardipine | Safety assessed by the incidence of myocardial infarction, death, Stroke, renal dysfunction. Assessment of Clevidipine efficacy using the analysis of the area under the curve of blood pressure normalized per hour. | Open prospective multicenter randomized clinical trial | USA | Not stated |
| Merry et al. | 2014 | Cardiac surgery intervened adult patients | 101 | Clevidipine 0.2–8 mcg/kg/min | Nitroglycerine 0.4mcg/kg/min to maximum dose | Assessment of Clevidipine efficacy using the analysis of the area under the curve of blood pressure | Multicenter randomized clinical trial. Not inferiority study | USA, New Zealand | The Medicines Company |

doi:10.1371/journal.pone.0150625.t001
infusion effect [37]. In patients scheduled for CABG who required postoperative anti-hypertensive therapy to maintain MAP between 70–80 mmHg, clevidipine showed greater preload, stroke volume, and cardiac output. On the other hand, heart rate and systemic vascular resistance were lower and there were not significant differences in regional myocardial oxygen consumption or oxygen extraction, regional myocardial lactate extraction or uptake, and myocardial blood flow when compared to sodium nitroprusside. For a normotensive individual, clevidipine decreased significantly regional myocardial oxygen extraction during infusion.

Table 2. Complications.

| Study              | Year | Intervention group complications | Intervention group severe complications | Control group complications | Control group severe complications |
|--------------------|------|----------------------------------|-----------------------------------------|-----------------------------|-----------------------------------|
| Powroznyk et al.   | 2003 | Not stated                        | Death as a consequence of mediastinal hemorrhage, not related with the study drug (1 patient 1.9%) | Not stated                 | Not stated                        |
| Levy et al. (ESCAPE-1) | 2007 | Fever 18.9%                      | Fever 13.7%                             | Myocardial infarction 2.9%  |
|                    |      |                                  | Atrial fibrillation 13.2%               |                             |
|                    |      |                                  | Acute renal dysfunction/failure 9.4%    | Acute renal dysfunction/failure 2.0% |
|                    |      |                                  | Nausea 5.7%                             | Nausea 9.8%                |
| Singla et al. (ESCAPE-2) | 2008 | Nausea 21.3%                     | Pneumonia, respiratory failure 3.3%     | Nausea 12.2%               | No stated                         |
|                    |      |                                  | Atrial fibrillation 21.3%               | Atrial fibrillation 12.2%, |
|                    |      |                                  | Insomnia 11.5%                          | Insomnia 6.1%,             |
|                    |      |                                  | Edema 8.2%                              | Edema 12.2%               |
|                    |      |                                  | Atelectasis 3.3%                        | Atelectasis 10.2,          |
| Aronson et al (ECLIPSE) | 2008 | Atrial fibrillation 2.4%         | Respiratory failure 1.1%                | Atrial fibrillation 2.4%,  |
|                    |      |                                  | Acute renal failure 2.3%                | Respiratory failure 2.5%,   |
|                    |      |                                  | Ventricular fibrillation 0.9%           | Acute renal failure 1.7%,   |
|                    |      |                                  | Cardiac arrest 0.5%                     | Ventricular fibrillation 1.5%, |
|                    |      |                                  | Stroke 0.5%                             | Cardiac arrest 1.1%,       |
|                    |      |                                  | Postoperative hemorrhage 0.5%           | Stroke 1.1%,               |
| Merry et al.       | 2014 | 63.3%                            | 6%                                      | 58.8%                      | Acute myocardial infarction 1%    |
|                    |      |                                  | Acute myocardial infarction 4%          | Atrial fibrillation 9.8%   |
|                    |      |                                  | Atrial fibrillation 2%                  |                             |

doi:10.1371/journal.pone.0150625.t002

Table 3. Drug-related Adverse Events.

| Study              | Year | Adverse events reported with clevidipine (%) | Type of adverse event reported with clevidipine |
|--------------------|------|-----------------------------------------------|------------------------------------------------|
| Powroznyk et al.   | 2003 | No                                            | No                                             |
| Levy et al. (ESCAPE-1) | 2007 | 9.4%                                          | No                                             |
| Singla et al (ESCAPE-2) | 2008 | 0.6%                                          | Thrombophlebitis                               |
| Aronson et al (ECLIPSE) | 2008 | 0%                                            | No                                             |
| Merry et al.       | 2014 | 0%                                            | No                                             |

doi:10.1371/journal.pone.0150625.t003
It also increased cardiac output and stroke volume by 10% without producing changes in the heart rate; coronary sinus blood flow increased 38% at the highest dose. [36, 38]

Two randomized, double-blind, placebo-controlled trials ESCAPE-1 and ESCAPE-2 demonstrated that clevidipine is appropriate and effective for the preoperative and postoperative BP management in hypertensive patients undergoing cardiac surgery [12, 13]. The reported incidence of treatment failure with clevidipine was 7.5% compared to 82.7% of placebo (per protocol rescue anti-hypertensive drug could be administered after treatment failure). No treatment failure as a consequence of lack of efficacy was observed in the clevidipine group [12, 13]. In patients treated with clevidipine, median time to target BP (reduction of systolic blood pressure ≥15% from baseline) was 6 minutes in the ESCAPE-1 and 5.3 minutes in the ESCAPE-2 trials. The ECLIPSE trials involved analysis of three parallel comparisons, prospective, randomized, open-label studies, performed in 61 medical centers. In this trial, patients undergoing cardiac surgery were randomized in a 1:1 ratio to receive clevidipine or one of three antihypertensive medications (nitroglycerin, sodium nitroprusside, or nicardipine) [14]. Mean area under the systolic blood pressure time curve revealed that clevidipine was more effective than nitroglycerin or sodium nitroprusside, sustaining the BP in the specified range in the perioperative setting. Additionally, in the postoperative setting, there was not a significant difference between clevidipine and nicardipine (Fig 5). In general, clevidipine was well tolerated when administered during the perioperative setting in patients who underwent cardiac surgery [13, 39].

The decrease in BP was associated to an increase in heart rate in healthy volunteers treated with clevidipine [33], with a slight increase in heart rate also in hypertensive patients who received clevidipine in a moderate dose. A modest increase in heart rate, and not reflex tachycardia, was observed in patients receiving clevidipine during cardiac surgery [12] or after coronary artery bypass grafting [38]. Clevidipine does not affect preload or venous capacitance, furthermore, as a dihydropyridine L-type calcium channel blocker clevidipine can produce a negative inotropic effect and potentially attenuate the reflex tachycardia triggered by its
administration and rapid upward titration. Reflex tachycardia can be secondary to vasodilation and decrease in blood pressure. However, the effect on heart rate and the possible mechanism associated to reflex tachycardia remain to be elucidated. [29] As shown by Aronson et al., 30 days mortality in patients treated with nitroprusside was greater when compared to patients treated with clevidipine (4.7% vs. 1.7%, p = 0.04). However, no significant difference in mortality was observed at 30 days for stroke, myocardial infarction, and renal failure [14].

Other studies, not included in this meta-analysis, are equally conclusive, in 2003, Powroznycyk et al. performed a randomized clinical trial in two medical centers in the United Kingdom comparing equivalent doses of clevidipine and nitroprusside [39]. In this study, they observed a greater heart rate increase with nitroprusside than with clevidipine (p < 0.001); nitroprusside significantly reduced the systolic volume and central venous pressure and required greater intravenous fluid administration. Nitroprusside also exposed a greater incidence of hypotension as adverse event [39].

In this meta-analysis, we have included the double-blind study performed in four different centers by Merry et al. [40]. This study demonstrated no inferiority of clevidipine when compared to nitroglycerin. Although, the global incidence of adverse event was similar in both

| Study or Subgroup | Clevidipine Events | Control Events | Risk Ratio M-H, Random, 95% CI Year | Risk Ratio M-H, Random, 95% CI |
|-------------------|-------------------|----------------|-------------------------------------|-------------------------------|
| Placebo           |                   |                |                                     |                               |
| Levy et al 2007   | 8                 | 53             | 1.28 [0.48, 3.44] 2007              |                               |
| Singlea et al 2008| 23                | 61             | 1.54 [0.86, 2.77] 2008              |                               |
| Subtotal (95% CI) | 114               | 100            | 1.47 [0.89, 2.43]                  |                               |
| Total events      | 31                | 18             |                                     |                               |
| Heterogeneity: Tau^2 = 0.00; Chi^2 = 0.10, df = 1 (P = 0.75); I^2 = 0% |
| Test for overall effect: Z = 1.49 (P = 0.14) |

**Table 1. Study results.**

| Antihypertensive | Clevidipine | Control | Risk Ratio M-H, Random, 95% CI Year |
|-------------------|-------------|---------|-------------------------------------|
| Aronson et al (NIC) 2008 | 55          | 752     | 0.66 [0.48, 0.92] 2008              |
| Merry et al 2014   | 8           | 53      | 1.28 [0.48, 3.44] 2014              |
| Subtotal (95% CI)  | 805         | 805     | 0.78 [0.45, 1.35]                   |
| Total events       | 63          | 89      |                                     |
| Heterogeneity: Tau^2 = 0.08; Chi^2 = 1.54, df = 1 (P = 0.21); I^2 = 35% |
| Test for overall effect: Z = 0.89 (P = 0.37) |

**Table 2. Antihypertensive results.**

| Study | Clevidipine Events | Control Events | Risk Ratio M-H, Random, 95% CI Year |
|-------|-------------------|----------------|-------------------------------------|
| Levy et al 2007 | 7              | 53             | 1.12 [0.40, 3.11] 2007              |
| Singlea et al 2008 | 13             | 61             | 1.74 [0.71, 4.24] 2008              |
| Aronson et al (NIC) 2008 | 18          | 752            | 1.00 [0.53, 1.91] 2008              |
| Merry et al 2014 | 1              | 49             | 0.21 [0.03, 1.72] 2014              |
| Total (95% CI)  | 915            | 905            | 1.09 [0.65, 1.83]                   |
| Total events     | 39             | 35             |                                     |
| Heterogeneity: Tau^2 = 0.04; Chi^2 = 3.53, df = 3 (P = 0.32); I^2 = 15% |
| Test for overall effect: Z = 0.34 (P = 0.73) |

**Figure 5. Forest Plot.** Safety. Forest plot considering p < 0.05 as statistically significant. One γ2 test was conducted for heterogeneity, considering p value of < 0.10 as statistically significant.

doi:10.1371/journal.pone.0150625.g005

**Figure 6. Forest Plot.** Atrial Fibrillation. Forest plot considering p < 0.05 as statistically significant. One γ2 test was conducted for heterogeneity, considering p value of < 0.10 as statistically significant. NIC, denotes nicardipine.

doi:10.1371/journal.pone.0150625.g006
### Summary of findings:

**Clevidipine compared to Placebo/Antihypertensive for perioperative hypertension control**

| Patient or population: | perioperative hypertension control |
|------------------------|------------------------------------|
| Setting:               | Perioperative care                 |
| Comparison:           | Clevidipine vs. Placebo/Antihypertensive |

#### Anticipated absolute effects (95% CI)

| Outcome                          | Relative effect (95% CI) | Anticipated absolute effects (95% CI) | Quality | What happens |
|----------------------------------|--------------------------|--------------------------------------|---------|--------------|
| **Effectiveveness**              |                          |                                      |         |              |
| versus placebo                    | RR 0.10 (0.05 to 0.18)   | Study population:                    |         |              |
| No of participants:              |                          | without Clevidipine:                 |         |              |
| 215 (2 RCTs)                     |                          | 812 per 1000 (41 to 146)             |         |              |
| With Clevidipino                 |                          | 81 per 1000 (41 to 146)              |         |              |
| **Difference**                   |                          | 731 fewer per 1000 (71 fewer to 666 fewer) |         |              |
| **Effectiveveness**              |                          |                                      |         |              |
| versus other antihypertensives    | -                        | The mean effectiveness versus other  |         |              |
| No of participants:              |                          | antihypertensives was 0              |         |              |
| 1507 (3 RCTs)                    |                          |                                      |         |              |
| **Safety**                       | RR 1.05 (0.63 to 1.77)   | Study population:                    |         |              |
| No of participants:              |                          | without Clevidipine:                 |         |              |
| 1824 (4 RCTs)                    |                          | 118 per 1000 (74 to 209)             |         |              |
| With Clevidipino                 |                          | 124 per 1000 (74 to 209)             |         |              |
| **Difference**                   |                          | 6 more per 1000 (44 fewer to 91 more) |         |              |
| **Atrial Fibrillation**          | RR 1.09 (0.65 to 1.83)   | Study population:                    |         |              |
| No of participants:              |                          | without Clevidipine:                 |         |              |
| 1820 (4 RCTs)                    |                          | 39 per 1000 (25 to 71)               |         |              |
| With Clevidipino                 |                          | 42 per 1000 (25 to 71)               |         |              |
| **Difference**                   |                          | 3 more per 1000 (14 fewer to 32 more) |         |              |

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).*

CI: Confidence interval; RR: Risk ratio; OR: Odds ratio;

**GRADE Working Group grades of evidence**

- **High quality**: We are very confident that the true effect lies close to that of the estimate of the effect.
- **Moderate quality**: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- **Low quality**: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
- **Very low quality**: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of the effect.

---

*Fig 7. GRADE. GRADE summary of findings table.*

doi:10.1371/journal.pone.0150625.g007

---

groups, arterial hypotension was more frequent in the group of patients treated with clevidipine (13 patients in clevidipine group vs. 8 in nitroglycerin group). Nevertheless, the double blinded (dummy) design of this trial was meant to be one of its strengths, but turned out to be a weakness, since it was more focused on the effectiveness of BP management rather than in its
safety. One of the limitations of this study was the small sample size (45 and 48 patients in the clevidipine and nitroglycerin group respectively) [40].

An exploratory post hoc analysis of the ECLIPSE trials has detected an increased 30 days mortality associated with perioperative systolic BP variability in patients who underwent cardiac surgery [5].

Regarding the rate of atrial fibrillation the comparative study of clevidipine to nicardipine, sodium nitroprusside and nitroglycerin showed no difference in the incidence of this event in between treatments [14].

The ESCAPE-1, patients in the placebo and clevidipine group, experienced increases in heart rate from a baseline of 71 beats per minute (bpm) and 76 bpm, respectively, to a maximal heart rate of 84 bpm in both groups [12]. None of the patients included in the ESCAPE-1 trial withdraw the study medication due to lack of safety. In the ESCAPE-2 trial, there was no evidence of reflex tachycardia. However, atrial fibrillation was more frequent in the clevidipine group (21.3% vs. 12.2%), and this was the reason why clevidipine was withdrawn in one of the patients enrolled in the study [13].

In the ECLIPSE trials, comparator treatment groups and clevidipine were associated with similar rates of adverse events [14]. The most common adverse event was atrial fibrillation that was present in all the groups of treatment. Nonetheless, our analysis did not demonstrate an increase in atrial fibrillation. Only one serious adverse event (thrombophlebitis in a patient treated with clevidipine) reported in the ESCAPE-2 trial was considered to be associated to the study drug administration. Additional serious adverse events were reported as unrelated to clevidipine. In the ESCAPE-1 trial, a greater incidence of acute kidney injury has been reported in the patients treated with clevidipine when compared to the patients treated with placebo plus standard rescue antihypertensive intravenous drug (9% vs. 2%, respectively) [12].

From the total analysis completed over the 1,824 patients included in prospective studies, the incidence of adverse events was 94 in the clevidipine group vs. 107 in the control group; this shows a non-significant risk reduction of 1.05 (C.I 0.63–1.77). Clevidipine, therefore, displayed a similar safety profile regarding the studied adverse events when compared to other medications. Additionally, clevidipine is useful for the treatment of perioperative hypertension, due to the clinically effective outcome, as clevidipine did not present a greater number of adverse events when compared to placebo (+rescue antihypertensive intravenous drug) (Fig 3 and Fig 6). In conclusion, this meta-analysis supports the use of clevidipine in maintaining the blood pressure in a prespecified range ((Decrease in SBP >15% of baseline per ESCAPE 2 study) in the perioperative setting of cardiac surgery patients experiencing hypertension. Our study shows that clevidipine is effective and at least safe, when compared with other intravenous alternatives for perioperative hypertension management in patients ≥18 years-old undergoing on- or off-pump valve replacement or repair and/or CABG, or, minimally invasive CABG surgery. Our results do not provide evidence of clevidipine use during pregnancy, patients with cerebrovascular accident within 3 months before clevidipine administration, left bundle branch block, permanent ventricular pacing, intolerance to calcium channel blockers, allergy to the lipid vehicle of clevidipine. Clevidipine administration should be done according to manufactures instructions and titrations should be done according to clinical criteria [25].

Limitations

There was moderate heterogeneity in the efficacy analysis in the group of studies that compare clevidipine with other antihypertensive agents (ECLIPSE), possibly due to the different characteristics of the comparators. Moreover, the number of patients and studies analyzed is very limited; and small studies tend to overestimate the effect.
Some studies could not be included as part of this meta-analysis due to methodological differences and other biases.

**Implications In Future Research**

Two other studies have shown the effectiveness of clevidipine against other vasodilators, however, these studies did not meet inclusion criteria, and hence probably the degree of evidence may increase with inclusion. Given the existent inconsistency, further studies that evaluate different outcomes are required (2015). A prospective multicentric randomized clinical trial designed to evaluate the efficacy and safety of clevidipine in the management of hypertension in non-cardiac surgeries, in critical care patients or patients’ experiencing hypertensive crisis or hypertensive emergencies is essential.

**Conclusions**

Clevidipine is an appropriate drug for the management of acute perioperative hypertension, unlike other intravenous infusions; clevidipine did not show adverse effects described with nitrites or tachyphylaxis. It has a short-acting effect; it is easy to titrate due to a linear dose-response and shows a rapid “wash-out” following a half-life of approximately 1 minute, which is an advantage over other calcium channel blockers.

Even though there is a wealth of data and the wide experience with other agents, clevidipine has several advantages that make it an ideal option for the perioperative use with a pharmacokinetic profile of rapid onset and short duration of action; efficacy data displayed limited excursions outside the desired BP range and lack of renal and hepatic metabolism.

**Supporting Information**

S1 PRISMA Checklist.

(DOC)

**Acknowledgments**

The EAR Group (www.eargroup.es) is an international research group within the Department of Pharmacology, Faculty of Medicine of the Complutense University of Madrid (Spain). Collaborative, nonprofit and exempt funding.

Teresa de la Torre Aragonés and Rocío Gálvez Lazcano (Infanta Leonor University Hospital Professional Library) collaborated as documentarians in the literature search.

**Author Contributions**

Conceived and designed the experiments: JMCV FLT SDB. Analyzed the data: JRM AE RCF AAG AZA. Wrote the paper: JRM AE RCF AZA. Data acquisition, analysis and interpretation; manuscript drafting, editing and submission: JRM AE RCF AZA. Abstracts review, evaluation of inclusion criteria and bias analysis: AAG AE. Design and coordination of the study and manuscript revision: JMCV FLT SDB.

**References**

1. Kumutala L, Sandhu G., Vandse R., Soghomonyan S., and Bergese SD. Innovative approaches to the management of acute arterial hypertension—clevidipine butyrate. Int J Anesthesiol. 2013; 1.4 (2013): 18–24.

2. Zuleta-Alarcon A, Castellon-Larios K, Bergese S. [The role of clevidipine in hypertension management: clinical results]. Rev Esp Anestesiol Reanim. 2014; 61(10):557–64. doi: [10.1016/j.redar.2014.06.006](https://doi.org/10.1016/j.redar.2014.06.006). PMID: [25236947](https://www.ncbi.nlm.nih.gov/pubmed/25236947).
3. Pollack CV Jr, Rees CJ. ACuTE CARE EVALuATIoN ANd MANAGEMENT. Emergency Medicine Cardiovascular Research and Education Group. 2008; 3.

4. Awad AS, Goldberg ME. Role of clevidipine butyrate in the treatment of acute hypertension in the critical care setting: a review. Vasc Health Risk Manag. 2010; 6:457–64. PMID: 20730061; PubMed Central PMCID: PMCPMC2922306.

5. Aronson S, Dyke CM, Levy JH, Cheung AT, Lumb PD, Avery EG, et al. Does perioperative systolic blood pressure variability predict mortality after cardiac surgery? An exploratory analysis of the ECLIPSE trials. Anesth Analg. 2011; 113(1):19–30. doi: 10.1213/ANE.0b013e31820f9231 PMID: 21346163.

6. Erickson AL, DeGrado JR, Fanikos JR. Clevidipine: a short-acting intravenous dihydropyridine calcium channel blocker for the management of hypertension. Pharmacotherapy. 2010; 30(5):515–28. doi: 10.1592/phco.30.5.515 PMID: 20412001.

7. van der Stroom JG, van Wezel HB, Langemeijer JJ, Koorsten HH, Kooymann J, van der Starre PJ, et al. A randomized multicenter double-blind comparison of urapidil and ketanserin in hypertensive patients after coronary artery surgery. J Cardiothorac Vasc Anesth. 1997; 11(6):729–36. PMID: 9327314.

8. Prlesi L, Cheng-Lai A. Clevidipine: a novel ultra-short-acting calcium antagonist. Cardiol Rev. 2009; 17(3):147–52. doi: 10.1097/CRD.0b013e31819fe23c PMID: 19384089.

9. Eisenberg MJ, Brox A, Bestawros AN. Calcium channel blockers: an update. Am J Med. 2004; 116(1):35–43. PMID: 14706664.

10. Bergese SD, Puente EG. Clevidipine butyrate: a promising new drug for the management of acute hypertension. Expert Opin Pharmacother. 2010; 11(2):281–95. doi: 10.1517/14656560903499293 PMID: 20088748.

11. Tulman DB, Stawicki SP, Papadimos TJ, Murphy CV, Bergese SD. Advances in management of acute hypertension: a concise review. Discov Med. 2012; 13(72):375–83. PMID: 22642919; PubMed Central PMCID: PMCPMC3727280.

12. Levy JH, Mancao MY, Gitter R, Kereiakes DJ, Grigore AM, Aronson S, et al. Clevidipine effectively and rapidly controls blood pressure preoperatively in cardiac surgery patients: the results of the randomized, placebo-controlled efficacy study of clevidipine assessing its preoperative antihypertensive effect in cardiac surgery-1. Anesth Analg. 2007; 105(4):918–25, table of contents. doi: 10.1213/ane.0b013e31820f9231 PMID: 17898366.

13. Singla N, Wartliet DC, Gandhi SD, Lumb PD, Sladen RN, Aronson S, et al. Treatment of acute postoperative hypertension in cardiac surgery patients: an efficacy study of clevidipine assessing its postoperative antihypertensive effect in cardiac surgery-2 (ESCAPE-2), a randomized, double-blind, placebo-controlled trial. Anesth Analg. 2008; 107(1):59–67. doi: 10.1213/ane.0b013e3181732e53 PMID: 18635468.

14. Aronson S, Dyke CM, Stierer KA, Levy JH, Cheung AT, Lumb PD, et al. The ECLIPSE trials: comparative studies of clevidipine to nitroglycerin, sodium nitroprusside, and nicardipine for acute hypertension treatment in cardiac surgery patients. Anesth Analg. 2008; 107(4):1110–21. doi: 10.1213/ane.0b013e3181732e53 PMID: 19631508.

15. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. J Clin Epidemiol. 2009; 62(10):1006–12. doi: 10.1016/j.jclinepi.2009.06.005 PMID: 19631508.

16. Higgins J, Green S. Cochrane handbook for systematic reviews of interventions version 5.1. 0. The Cochrane Collaboration, 2011. 2013.

17. Jakobsen JC, Wettevold J, Winkel P, Lange T, Gluud C. Thresholds for statistical and clinical significance in systematic reviews with meta-analytic methods. BMC Med Res Methodol. 2014; 14:120. doi: 10.1186/1471-2288-14-120 PMID: 25416419; PubMed Central PMCID: PMCPMC4251848.

18. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic reviews and meta-analyses protocols (PRISMA-P) 2015 statement. Syst Rev. 2015; 4:1. doi: 10.1186/2046-4053-4-1 PMID: 25554246; PubMed Central PMCID: PMCPMC4320440.

19. Review Manager [RevMan] [Computer program]. Version 5.2. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2012.

20. Wallace BC, Dahabreh IJ, Trikalinos TA, Lau J, Trow P, Schmid CH. Closing the gap between methodologists and end-users: R as a computational back-end. J Stat Softw. 2012; 49(5):1–15.

21. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986; 7(3):177–88. PMID: 3802633.

22. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003; 327(7414):557–60. doi: 10.1136/bmj.327.7414.557 PMID: 12958120; PubMed Central PMCID: PMCPMC192859.
23. Neumann I, Pantoja T, Penaloza B, Cifuentes L, Rada G. [The GRADE system: a change in the way of assessing the quality of evidence and the strength of recommendations]. Rev Med Chil. 2014; 142 (5):630–5. doi: 10.4067/S0034-98872014000500012 PMID: 25427021.

24. Jakobsen JC, Gluud C, Winkel P, Lange T, Wetterslev J. The thresholds for statistical and clinical significance—a five-step procedure for evaluation of intervention effects in randomised clinical trials. BMC Med Res Methodol. 2014; 14:34. doi: 10.1186/1471-2288-14-34 PMID: 24588900; PubMed Central PMCID: PMCPMC4015863.

25. Levy JH. The ideal agent for perioperative hypertension and potential cytoprotective effects. Acta Anaesthesiol Scand Suppl. 1993; 99:20–5. PMID:8480502.

26. Desai RG, Muntazar M, Goldberg ME. Strategies for managing perioperative hypertension. Curr Hypertens Rep. 2009; 11(3):173–7. PMID:1944325.

27. Varon J. Treatment of acute severe hypertension: current and newer agents. Drugs. 2008; 68(3):283–97. PMID:18257607.

28. Padilla Ramos A, Varon J. Current and newer agents for hypertensive emergencies. Curr Hypertens Rep. 2014; 16(7):450. doi: 10.1007/s11906-014-0450-z PMID: 24863753.

29. Cleviprex (clevidipine butyrate) [package insert]. Parsipanny NT, 2008 MC.

30. Ericsson H, Schwieler J, Lindmark BO, Lofdahl P, Thulin T, Regardh CG. Enantioselective pharmacokinetics of the enantiomers of clevidipine following intravenous infusion of the racemate in essential hypertensive patients. Chirality. 2001; 13(3):130–4. doi: 10.1002/1520-636X(2001)13:3<130::AID-CHIR1009>3.0.CO;2-N PMID: 11270321.

31. Ericsson H, Tholander R, Regardh CG. In vitro hydrolysis rate and protein binding of clevidipine, a new ultrashort-acting calcium antagonist metabolised by esterases, in different animal species and man. Eur J Pharm Sci. 1999; 8(1):29–37. PMID:10072476.

32. Ericsson H, Fakt C, Jolin-Mellgard A, Nordlander M, Sohtell L, Sunzel M, et al. Clinical and pharmacokinetic results with a new ultrashort-acting calcium antagonist, clevidipine, following gradually increasing intravenous doses to healthy volunteers. Br J Clin Pharmacol. 1999; 47(5):531–8. PMID:10336577; PubMed Central PMCID: PMCPMC2014189.

33. Ericsson H, Fakt C, Hoglund L, Jolin-Mellgard A, Nordlander M, Sunzel M, et al. Pharmacokinetics and pharmacodynamics of clevidipine in healthy volunteers after intravenous infusion. Eur J Clin Pharmacol. 1999; 55(1):61–7. PMID:10206087.

34. Schwieler JH, Ericsson H, Lofdahl P, Thulin T, Kahan T. Circulatory effects and pharmacology of clevidipine, a novel ultra short acting and vascular selective calcium antagonist, in hypertensive humans. J Cardiovasc Pharmacol. 1999; 34(2):268–74. PMID:10445679.

35. Murphy Cv, Brower Kl. Safety and Efficacy of Intravenous Clevidipine for the Perioperative Control of Acute Hypertension. Clinical Medicine Insights Therapeutics. 2011; 3.

36. Nordlander M, Sjöquist PO, Ericsson H, Ryden L. Pharmacodynamic, pharmacokinetic and clinical effects of clevidipine, an ultrashort-acting calcium antagonist for rapid blood pressure control. Cardiovasc Drug Rev. 2004; 22(3):227–50. PMID:15492770.

37. Hersey SL, O’Dell NE, Lowe S, Rasmussen G, Tobias JD, Deshpande JK, et al. Nicardipine versus nitroprusside for controlled hypotension during spinal surgery in adolescents. Anesth Analg. 1997; 84 (6):1239–44. PMID:9174299.

38. Kieler-Jensen N, Jolin-Mellgard A, Nordlander M, Ricksten SE. Coronary and systemic hemodynamic effects of clevidipine, an ultra-short-acting calcium antagonist, for treatment of hypertension after coronary artery surgery. Acta Anaesthesiol Scand. 2000; 44(2):186–93. PMID:10695913.

39. Powroznik AV, Vuylsteke A, Naughton C, Misso SL, Holloway J, Jolin-Mellgard A, et al. Comparison of clevidipine with sodium nitroprusside in the control of blood pressure after coronary artery surgery. Eur J Anaesthesiol. 2003; 20(9):697–703. PMID:12974590.

40. Merry AF, Avery EG, Nussmeier NA, Playford HR, Warman GR, Wang Y, et al. Clevidipine compared with nitroglycerin for blood pressure control in coronary artery bypass grafting: a randomized double-blind study. Can J Anaesth. 2014; 61(5):398–406. doi: 10.1007/s12630-014-0131-z PMID: 24700403.