A Prospective, Open-Label Trial of Clevidipine for Controlled Hypotension During Posterior Spinal Fusion

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OBJECTIVES: Controlled hypotension is one means to limit or avoid the need for allogeneic blood products. Clevidipine is a short-acting, intravenous calcium channel antagonist with a half-life of 1 to 3 minutes due to rapid metabolism by non-specific blood and tissue esterases. To date, there are no prospective evaluations with clevidipine in the pediatric population. We prospectively evaluated the dosing requirements, efficacy, and safety of clevidipine for controlled hypotension during spinal surgery for neuromuscular scoliosis in the pediatric population.

METHODS: Patients undergoing posterior spinal fusion for neuromuscular scoliosis were eligible for inclusion. The study was an open label, observational study. Maintenance anesthesia included desflurane titrated to maintain a bispectral index at 40 to 60 and a remifentanil infusion. Motor and somatosensory evoked potentials were monitored intraoperatively. When the mean arterial pressure (MAP) was ≥ 65 mmHg despite remifentanil at 0.3 mcg/kg/min, clevidipine was added to maintain the MAP at 55 to 65 mmHg. Clevidipine was initiated at 0.25 to 1 mcg/kg/min and titrated up in increments of 0.25 to 1 mcg/kg/min every 3 to 5 minutes to achieve the desired MAP.

RESULTS: The study cohort included 45 patients. Fifteen patients (33.3%) did not require a clevidipine infusion to maintain the desired MAP range, leaving 30 patients including 13 males and 17 females for analysis. These patients ranged in age from 7.9 to 17.4 years (mean ± SD: 13.7 ± 2.2 years) and in weight from 18.9 to 78.1 kg (mean ± SD: 43.4 ± 14.2 kg). Intraoperatively, the clevidipine infusion was stopped in 6 patients as the surgeon expressed concerns regarding spinal cord perfusion and requested a higher MAP than the study protocol allowed. The data until that point were included for analysis. The target MAP was initially achieved at a mean time of 8.9 minutes. Sixteen of the 30 patients (53.3%) achieved the target MAP within 5 minutes. Heart rate (HR) increased from a baseline of 83 ± 16 to 86 ± 15 beats per minute (mean ± SD) (p=0.04) with the administration of clevidipine. No patient had a HR increase ≥ 20 beats per minute or required the administration of a β-adrenergic antagonist. The duration of the clevidipine administration varied from 8 to 527 minutes (mean ± SD: 160 ± 123 minutes). The maintenance infusion rate of clevidipine varied from 0.25 to 5.0 mcg/kg/min (mean ± SD: 1.4 ± 1.1 mcg/kg/min). Clevidipine was paused a total of 43 times in the 30 cases. In 18 of the 30 patients (60%), the clevidipine infusion was temporarily paused more than once due to a MAP < 55 mmHg. A fluid bolus was administered to only 1 patient to treat the low MAP. No patient required the administration of a vasoactive agent for hypotension. When the clevidipine infusion was discontinued as controlled hypotension was no longer required, the MAP returned to baseline or ≥ 65 mmHg within 10 minutes in 12 of the 30 patients (40%).

CONCLUSIONS: Clevidipine can be used to provide controlled hypotension during posterior spinal fusion. The response of the MAP, both the onset and duration of action, were rapid. Although titration of the infusion with occasional pauses of administration may be needed, excessive hypotension was not noted.

INDEX TERMS: clevidipine, controlled, hypotension, orthopedic surgery, spinal fusion

INTRODUCTION

Various techniques have been suggested as a means of limiting or avoiding the need for allogeneic blood transfusions during major orthopedic surgical procedures. Controlled hypotension is a technique that involves the use of pharmacological agents to lower the mean arterial pressure (MAP) to 50 to 65 mmHg. Despite the availability of several different agents to provide controlled hypotension including direct-acting vasodilators (sodium nitroprusside, nitroglycerin), calcium channel antagonists (nicardipine), β-adrenergic antagonists, ganglion blocking agents, and the inhalational anesthetic agents, none has gained universal use. Sodium nitroprusside can result in profound hypotension and is frequently associated with rebound tachycardia, which may require the addition of a second agent such as propranolol or esmolol. The calcium channel antagonist, nicardipine, which dilates primarily the arterial side of the vasculature, offers the advantage of less rebound tachycardia and a lower incidence of excessive hypotension. However, given its longer half-life, titration may be slower than a rapid-acting agent like sodium nitroprusside. Additionally, the duration of action is markedly longer thereby being problematic should inadvertent hypotension occur.

Clevidipine (Cleviprex, The Medicines Company, Parsippany, NJ) is a short-acting, intravenous calcium channel antagonist with a half-life of 1 to 3 minutes due to rapid metabolism by non-specific blood and tissue esterases. It is currently approved by the Food and Drug Administration for the reduction of blood pressure (BP) in adults when oral therapy is not feasible or desirable. The majority of experience with this novel agent has been in the control of perioperative BP in adults. Preliminary data have also demonstrated the safety and efficacy of clevidipine in the pediatric population following cardiac surgery for congenital heart disease, as well as controlled hypotension during spinal surgery. To date, there are no prospective evaluations with the use of clevidipine in the pediatric population. The current study prospectively evaluates the dosing requirements, efficacy, and adverse effect profile of clevidipine for controlled hypotension during spinal surgery in the pediatric population.

METHODS

This study was an open label, observational study in a single institution (Nationwide Children’s, Columbus, OH) to assess the effects of clevidipine to control BP and provide controlled hypotension during posterior spinal fusion. The study was approved by the Institutional Review Board of Nationwide Children’s, Columbus, Ohio (IRB12-00261), which waived requirements for informed consent due to the observational nature of the study, no significant change in our current practice, and no additional risk to the patient. The study was registered at ClinicalTrials.gov (NCT01645111). Patients less than 18 years of age undergoing posterior spinal fusion for neuromuscular scoliosis in which controlled hypotension was planned for the operative care were eligible for inclusion. Patients with idiopathic scoliosis were excluded from the current study because they were included in another ongoing study.

There was no change in the standard and usual anesthetic care including premedication, anesthetic induction, intraoperative anesthetic management, and intraoperative monitoring. All patients were held nil per os according to guidelines of the American Society of Anesthesiologists (ASA). Premedication with oral or intravenous midazolam was administered based on the clinical needs of the patient. The patient was brought to the operating room and standard ASA monitors were applied. Anesthesia was induced with inhalational or intravenous agents based on the preference of the patient. Endotracheal intubation was facilitated with a single dose of rocuronium (0.3 mg-0.4 mg/kg). For each case, there were 2 large bore peripheral intravenous cannulae and an arterial cannula. Motor and somatosensory evoked potentials were monitored intraoperatively in all cases. Maintenance of anesthesia was based on our usual practice for these cases as has been previously reported. The technique included desflurane titrated to maintain a bispectral index at 40 to 60 and fentanyl 2 to 4 mcg/kg followed by a remifentanil infusion to maintain the MAP at 55 to 65 mmHg. Additional techniques to limit the need for allogeneic blood products included tranexamic acid and intraoperative blood salvage.

If the MAP was ≥ 65 mmHg despite a remifentanil infusion at 0.3 mcg/kg/min, clevidipine was
added to maintain the MAP at 55 to 65 mmHg. Clevidipine was initiated at 0.25 to 1 mcg/kg/min and titrated up in increments of 0.25 to 1 mcg/kg/min every 3 to 5 minutes to achieve the desired MAP. Vital signs including heart rate (HR) and BP were recorded on the data sheet when clevidipine was started, at the time that the target MAP was achieved, and then at 30-minute increments thereafter. Primary end points for the study were time to achieve the target MAP, overall efficacy of clevidipine (percentage of patients in which successful controlled hypotension was achieved), and dose required to provide controlled hypotension. Adverse effects attributable to clevidipine including excessive hypotension, the need to pause the clevidipine infusion, the need to administer a vasoactive agent, or the need to give a fluid bolus were recorded as safety end points.

As this was an open label trial, there was no comparator group. However, the baseline HR was compared to subsequent HRs using an analysis of variance with p<0.05 considered significant. Arterial blood gases obtained during the case were compared to the original value using an analysis of variance to determine effects on oxygenation related to the use of a vasodilator and its resultant effects on ventilation-perfusion matching. Unless otherwise noted, data are present as mean ± SD.

RESULTS

The study cohort included 45 patients. Fifteen patients (33.3%) did not require a clevidipine infusion to maintain the desired MAP range, leaving 30 patients including 13 males and 17 females for analysis. These patients ranged in age from 7.9 to 17.4 years (13.7 ± 2.2 years) and in weight from 18.9 to 78.1 kg (43.4 ± 14.2 kg). The etiologies of the spinal deformity and comorbid conditions included neuromuscular, Arnold-Chiari malformation, cerebral palsy, tethered cord, myelomeningocele, congenital kyphosis, spinal muscle atrophy, muscular dystrophy, and Conradi-Henemann syndrome. Several patients had multiple causes of the spinal deformity.

Intraoperatively, the clevidipine infusion was discontinued in 6 of the 30 patients due to concerns regarding spinal cord perfusion related to the severity of the spinal cord deformity. In 3 of these 6 patients, the return of the MAP to baseline was requested based on the clinical judgment of the surgeon. In the other 3 patients, the MAP was allowed to return to baseline due to changes in neurophysiological monitoring. These changes reverted to baseline promptly with the restoration of BP. Until the time that controlled hypotension was discontinued, the data from these patients were included for analysis.

The target MAP was initially achieved at 8.9 ± 10.8 minutes (median time of 5 minutes). More than half of the 30 patients (53.3%) achieved the target MAP within 5 minutes. In 1 patient, the target MAP was not achieved with a clevidipine infusion at 5 mcg/kg/min and labetalol was required to achieve the desired BP (see discussion). With the administration of clevidipine to this cohort, the HR increased from a baseline of 83 ± 16 to 86 ± 15 beats per minute (p=0.04). None of patients had an HR increase ≥ 20 beats per minute or required the administration of a β-adrenergic antagonist to control HR. The duration of the clevidipine administration varied from 8 to 527 minutes (160 ± 123 minutes). The maintenance infusion rate of clevidipine varied from 0.25 to 5.0 mcg/kg/min (1.4 ± 1.1 mcg/kg/min).

In 18 of the 30 patients (60.0%), the clevidipine infusion was discontinued temporarily at least once due to a MAP < 55 mmHg. The number of pauses per patient varied from 1 to 5 for a total of 43 in the entire cohort. During these pauses and the low MAP, the only intervention required at the discretion of the attending anesthesiologist was the administration fluid bolus (4-5 mL/kg) in 1 patient. No patient required the administration of a vasoactive agent for excessive hypotension due to clevidipine. When comparing the 18 patients who had a low MAP (Group MAP < 55) with the other 12 patients whose MAP stayed within the desired range (Group MAP ≥55), there were no significant difference in age and weight. However, anesthesia time, surgical time, and the number of segments of fused were significantly greater in the patients who required a temporary pause of the clevidipine infusion (Table).

When the clevidipine infusion was finally discontinued when controlled hypotension was no longer required, the MAP returned to ≥ 65 mmHg within 10 minutes in 12 of the 30 patients (40.0%). Seven patients (23%) received blood transfusion, and 21 patients (71%) received colloid administration. In 15 patients, an arterial blood gas analysis was available both before the clevidipine and after the initiation of the clevidip-
ine. No change in oxygenation (P_{O2}/F_{O2} ratio: P/F ratio) was noted (539 ± 46 mmHg vs. 541 ± 73 mmHg, p=0.46).

DISCUSSION

Several techniques have been evaluated to determine their efficacy in limiting intraoperative blood loss to eliminate the allogeneic blood products use. Controlled hypotension is a commonly used technique that has been shown to be effective in various surgical procedures including major orthopedic procedures such as posterior spinal fusion. Despite the availability of several pharmacologic agents for controlled hypotension, concerns have been expressed with all of these agents. Clevidipine is a short-acting, intravenous calcium channel antagonist, undergoing rapid metabolism by non-specific blood and tissue esterases with a half-life of 1 to 3 minutes. Its hemodynamic profile is similar to that of nicardipine with a preferential effect on the arterial versus the venous vasculature thereby limiting its effects on preload and HR. Unlike nicardipine, the rapid metabolism of clevidipine allows its easy titration by continuous infusion as well as provides a short duration of action should adverse effects occur. Clevidipine is provided in a lipid-based solution similar to propofol. Even with prolonged infusions or when coadministered with propofol, the preliminary data do not seem to indicate that there is a risk of significant elevation of serum triglyceride levels. However, the administration of clevidipine is relatively contraindicated in patients with allergies to soybeans, soy products, eggs, or egg products or acquired and inherited disorders of lipid metabolism.

For the first time, the current study prospectively investigated the efficacy of clevidipine in the pediatric population. In the current study, clevidipine was used for the provision of controlled hypotension during posterior spinal fusion in the pediatric population as a technique to limit the need for allogeneic blood transfusion. Clevidipine achieved the target MAP within 10 minutes in 70.0% of patients with the average time of 8.9 minutes and a median time of 5 minutes. One patient required 51 minutes to achieve the target MAP and the administration of labetalol despite clevidipine at 5 mcg/kg/min. This patient was a comorbid condition requiring the chronic administration of methylphenidate and aripiprazole, which may have interfered with the efficacy of clevidipine. Although the average HR increase of 3 beats per minute after the initiation of the clevidipine infusion reached statistical significance, it was within a clinically acceptable range and there was no requirement for treatment. No patient received a β-adrenergic antagonist to control HR.

In 18 of the 30 patients, a pause in the clevidipine infusion was necessary due to a lower than desired MAP. Of note, the need to pause

| Table. Comparison of Patients Who Had a MAP < 55 mmHg Versus Those Who Did Not |
|---------------------------------|---------------------------------|-----------------|
| Group MAP < 55 mmHg (n=18) | Group MAP ≥ 55 mmHg (n=12) | p-Value |
| Sex (Male/Female) | 9/9 | 4/8 | — |
| Age (yr) | 13.9 ± 2.6 | 13.5 ± 1.7 | 0.57 |
| Body weight (kg) | 43.1 ± 16.4 | 43.8 ± 10.8 | 0.89 |
| ASA (1/2/3/4) | 0/3/14/1 | 0/2/9/1 | — |
| Anesthesia time (min) | 519 ± 127 | 362 ± 75 | 0.0004 |
| Surgical time (min) | 415 ± 121 | 266 ± 65 | 0.0002 |
| Segment of fusion | 14.1 ± 3.8 | 10.6 ± 4.2 | 0.048 |
| MAP at initiation of clevidipine (mmHg) | 73.1 ± 9.3 | 74.5 ± 10.7 | 0.72 |
| HR at initiation of clevidipine (bpm) | 83.3 ± 16.0 | 82.1 ± 16.4 | 0.85 |
| HR when target MAP achieved (bpm) | 85.9 ± 13.8 | 85.8 ± 16.1 | 0.99 |
| Time to achieve target MAP (min) | 6.7 ± 7.9 | 12.2 ± 13.8 | 0.23 |
| Clevidipine dose when target MAP achieved (mcg/kg/min) | 1.3 ± 0.8 | 1.9 ± 1.7 | 0.28 |
| Total clevidipine time (min) | 176 ± 141 | 135 ± 92 | 0.35 |

bpm, beats per minute; HR, heart rate; MAP, mean arterial pressure
Data are displayed as mean ± SD or absolute values. P value <0.05 indicates significant difference.
the infusion tended to occur in longer and more complex cases as the anesthesia time, surgical time, and the number of segments of fused were significantly greater in the patients who required a temporary pause of the clevidipine infusion. Given its nature of short duration of action, the MAP returned to the target range without treatment except in 1 patient who received a fluid bolus. This fluctuation in BP is not surprising given the comorbid conditions of the patients in the current cohort. Additionally, these patients were undergoing a major orthopedic surgical procedure, which can result in blood loss and shifting intravascular volumes. In this setting, the use of a short-acting agent such as clevidipine offers an advantage, as its effects will rapidly dissipate once the infusion is discontinued.

When focusing on the cases in which the clevidipine infusion was discontinued with the completion of the controlled hypotension, the mean time of MAP return to baseline (7.2 ± 6.7 minutes) was shorter than that reported from other studies with nicardipine (18.1 ± 13.5 minutes,4 26.8 ± 4.0 minutes,5 median of 66.5 minutes6) and nitroprusside (7.3 ± 1.1 minutes,5 median of 20.0 minutes7).

In a previous study, Tobias et al15 retrospectively reviewed the use of clevidipine for controlled hypotension in 20 adolescents during anterior and posterior spinal fusion. When compared to the results of this previous study, we noted a longer time to achieve the target MAP, lower dosing requirement, and less increase in HR. The smaller initial dose and smaller incremental change in the dose of clevidipine in our study likely accounts for these results (minimal starting dose of 0.25 mcg/kg/min versus 0.5 mcg/kg/min). Due to the protocol of our current study, the infusion was increased no more frequently than every 3 to 5 minutes, and while given the retrospective nature of the previous study, dosing was not rigorously controlled. Furthermore, if a more rapid onset is desired, the infusion can be started at a larger dose or the infusion rate can be increased more rapidly. The average infusion rate of the previous retrospective study was also higher than the current cohort of patients (1.4 ± 1.1 mcg/kg/min vs. 2.9 ± 0.7 mcg/kg/min). The previous retrospective study included both idiopathic and neuromuscular scoliosis patients. As the idiopathic patients are generally free of comorbid diseases, we would postulate that this may account for the dosing differences. However, these data also illustrate that there may be significant interpatient variability in dosing requirements for such agents. The easy titratability of clevidipine is another advantage as rapid dose adjustments can be made to provide the effective dose regardless of this interpatient variability. Given that the reflex tachycardia is dose-related, the larger dose requirements in our previous study would also explain the differences in the HR response between the 2 studies.

Although, the main outcome that should be used to evaluate the efficacy of an agent for controlled hypotension is intraoperative blood loss and the need for allogeneic transfusions, estimated blood loss is affected by several factors including type of scoliosis, degree of curvature, lumbosacral fusion, patient’s body weight, and the length of surgical procedure. Since there was no control group in the current study, we cannot comment on the efficacy of clevidipine in regard to blood loss when compared directly with other agents.17,18 However, given that the current cohort of patients includes those with neuromuscular scoliosis receiving long segment of fusion (average of 12.8 ± 4.3 segments) with a high rate of lumbosacral fusion (40%), the estimated blood loss in the current study (434 ± 248 mL) seems reasonably less compared to the previous studies investigating other agents.3–7,10,15 Also, the number of patients who received allogeneic transfusions was acceptably small in the current study (7 of 30 patients, 23%). An additional limitation of the current study is that there was no defined indication for blood transfusion or transfusion trigger as a part of the study protocol.

Another theoretical concern with use of clevidipine includes a potential effect on oxygenation due to its direct vasodilating effect with inhibition of hypoxic pulmonary vasoconstriction, which affects ventilation-perfusion matching. In the current study, the oxygenation was not significantly changed with the clevidipine infusion compared to the baseline (mean P/F ratio, 539 ± 46 mmHg vs. 541 ± 73 mmHg, p=0.46), which is similar to the findings in the previous study.11

In summary, clevidipine can be used as an effective agent to provide controlled hypotension during posterior spinal fusion during anesthesia consisting of desflurane and remifentanil. The response of the MAP, both the onset and offset, were rapid. The short duration of action was ben-
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...as its discontinuation was required in 6 of the 30 patients due to concerns regarding spinal cord perfusion related to the severity of the spinal cord deformity. Furthermore, this short duration of action would be beneficial during major orthopedic surgical procedures where rapid blood loss and fluid shifts can result in hypotension especially in patients with comorbid conditions. Although titration of the infusion with occasional pauses of administration may be needed, excessive hypotension was not noted in the current study. The only hemodynamic change we noted was a slight increase in HR. This phenomenon is likely dose related, and a greater increase in HR may be expected if larger doses are required.

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Abbreviations ASA, American Society of Anesthesiologists; BP, blood pressure; HR, heart rate; MAP, mean arterial pressure; P/F ratio, PaO₂/FIO₂ ratio

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