Hemodynamic effects of epidural clonidine at patients undergoing lung surgery

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Abtract

Background and Purpose: *Clonidine is an α_2-adrenergic agonist which can be used as an adjuvant in epidural drug mixture and is interesting for its diverse responses, including analgesia and sympatholysis. Many surveys reported contradictory hemodynamic effects of clonidine. We wanted to determine if postoperative epidural clonidine causes hemodynamic instability in patients undergoing lung surgery. We were interested in hypotension and bradycardia and required administration of additional i.v. fluids or drugs during early postoperative period.*

Materials and Methods: *In a prospective randomized double-blinded study we enrolled 24 patients with lung carcinoma scheduled for thoracotomy. They were randomly assigned to morphine group (M) or clonidine group (C). Before operation we inserted an epidural catheter at level T6-7. Group-M received a bolus of 40 μg/kg of morphine in 10 mL saline and group-C additionally to that 4 μg/kg of clonidine. For postoperative analgesia we used a mixture of 4 μg/kg/h of morphine and 10 μg/kg/h of bupivacain in saline for group-M, and additionally to that 0.2 μg/kg/h of clonidine for group-C. Blood pressure, heart rate, amount of fluids and atropine given were monitored during operation and throughout the first 42 hours after operation.*

Results: *The results of this trial demonstrate a marked reduction in systolic, diastolic and mean arterial pressure as well as heart rate throughout the early postoperative study period in group-C. Hypotension demanded treatment with i.v. fluids.*

Conclusion: *High thoracic epidural clonidine used for postoperative analgesia in patients undergoing lung surgery lowers the heart rate and causes hypotension.*

INTRODUCTION

Epidural analgesia is used for several years for perioperative pain control in major surgery. Clonidine is an α_2 adrenergic agonist which can be used as an adjuvant in epidural drug mixture *(1)*. α_2 agonists produce diverse responses, including analgesia, anxiolysis, sedation and sympatholysis (2). The site for the actions is centrally in the brain steam and the spinal cord as well as peripherally at sympathetic nerve terminals and on receptors located on smooth muscles cells in the resistant vessels *(2, 3)*. Clonidine as an adjunct in epidural drug mixture is interesting for its analgesic as well as sympatholytic effects, which present as lower blood pressure and heart rate.

Perioperative epidural analgesia in lung surgery patients is one of the techniques that probably contributed to a decline in postoperative pulmonary complications such as atelectasis and pneumonia *(4)*.

Perioperative fluid management in patients after lung surgery should be restrictive, since early excessive fluid administration is recognized as significant risk factor for postoperative acute lung injury (ALI) in these patients *(5)*.

On our thoracic surgery ward we used a mixture of morphine, bupivacaine and clonidine for epidural perioperative analgesia. In this research we wanted to determine if epidural clonidine causes hemodynamic instability which would present as hypotension and bradycardia and thus requiring us to administer additional i.v. fluids or drugs during early postoperative period at patients undergoing lung surgery.

MATERIALS AND METHODS

In a prospective randomized double-blinded study we enrolled 24 patients with lung carcinoma and ASA physical status 2–3. They were all undergoing thoracotomy for a different type of lung surgery: pulmectomy, lobectomy or explorative operation. Patients with history of diabetes mellitus, autoimmune disease, receiving α or β adrenergic agonists or antagonists, metildopa, corticosteroids, antihistaminics, nonsteroidal antireumatics or transfusion were not included in the study.

Patients gave a written informed consent before the surgery. The study was approved by Ethical Committee at Ministry of health of Slovenia. We randomly distributed the patients in two groups, C – clonidine and M – morphine group (12 patients in each group). They were followed up during the operation and for 42 hours postoperatively in the intensive care unit (ICU).

All patients were premedicated with oral diazepam 0.1–0.2 mg/kg 1 h before arriving to the operating room. After coming to the operating room, all patients received an intravenous and intra-arterial line (cubital vein and radial artery). They received midazolam 0.05 mg/kg i.v. Before induction into general anaesthesia an epidural catheter (EC) at level T6-7 was inserted and a test dose of 4 mL of 2% lydocaine (80 mg) was introduced through it. After the level of epidural block was confirmed with cold-warm technique, M group received a bolus of 40 μg/kg of morphine in 10 mL saline through the EC and C group received a bolus of 4 μg/kg of clonidine and 40 μg/kg of morphine in 10 mL saline. After 20 minutes induction into general anaesthesia followed with propofol 1–2 mg/kg, fentanyl 1.5 μg/kg and vecuronium 0.1 mg/kg. All patients were endotracheally intubated with double-lumen tube. General anaesthesia was maintained with 6–12 mg/kg/h of propofol and fentanyl and vecuronium if needed. Low blood pressure was corrected with volume load (colloids or crystalloids), atropine was used for low heart rate. The patients were ventilated with oxygen/air mixture (FiO$_2$ 0.3–0.6). When only half of the lungs were ventilated, we used FiO$_2$ of 1. All patients were extubated in the operating room.

Approximately ½ an hour before the end of operation postoperative analgesia pump was connected to epidural catheter. Group M received 4 μg/kg/h of morphine and 10 μg/kg/h of bupivacaine in saline mixture, group C received 0.2 μg/kg/h of clonidine, 4 μg/kg/h of morphine and 10 μg/kg/h of bupivacaine in saline mixture. Epidural drug mixture in group M consisted of 10 mg morphine and 25 mg bupivacaine in up to 100 mL saline, and in group C it consisted of 10 mg morphine, 25 mg bupivacaine and 0.5 mg clonidine in up to 100 mL of saline. Continious postoperative infusion through EC at constant rate was used throughout the postoperative observing time. No bolus doses were allowed. At VAS > 3, piritramid 3–5 mg i.v. was given in both groups. Analgesia through EC remained in place in average 4.1 days (3–5 days), when it was replaced with other medication. During the first 42 hours after surgery patients recived no other analgetics but the ones described.

During the study period of first 42 hours after operation and admision to ICU blood pressure and heart rate were monitored each hour as well as the amount of fluids and atropine given to the patients. The policy of the thoracic surgery ward was to give 1500 mL of crystalloid fluids on the day of operation and the first postoperative day and additionally if needed according to blood pressure and central venous pressure measurements. Additional i.v. colloid fluids were prescribed when systolic blood pressure dropped under 100 mmHg. The need for more than standard amount of i.v. was determined by surgeons. Atropine was administered when heart rate fell bellow 45 beats per minute. Patients were given fluids orally on first postoperative day as demanded. Intraoperative blood loss, fluid and atropine administration was also recorded.

Statistical analysis

Nominal data (i.e. gender and ASA physical status) were analyzed by ordinary chi-square test or Fisher's exact test if any expected cell frequency was lower than 5. Basic comparisons between analgesic groups (morphine vs. clonidine) were done with independent samples *t*-test (when necessary, we used the correction for unequal group variances). Effects of analgesic type (morphine vs. clonidine) and time course of treatment on blood pressure and heart rate were analyzed by two-way mixed analysis of covariance (analgesic type as a fixed factor, time course as repeated measures factor, body mass index and postoperative colloid intake as covariates). When reporting the results of analysis of covariance, the meaning of abbreviations used is as follows: *MSE*: mean squared error, *F*: F statistic (a ratio between effect variance and error variance), which is used to asses statistical significance of main (and interaction) effects. Beside pair-wise comparisons for each time point (*t*-tests with Bonferroni correction for multiple comparisons) we also computed Cohen's *d* as a measure of effect size. All statistical tests were done at alpha-error of.05 (effects with *p* values less than.05 were considered statistically significant).

RESULTS

There were no statistically significant differences in age, gender, ASA physical status, duration of anaesthesia, blood loss during operation, intra- and postoperative crystalloid intake, intraoperative colloid intake and postoperative oral fluid intake between the groups. The groups differed statistically significant in body mass index and colloid intake in ICU and in the first 24 to 27 hours (Table 1). Three patients from the C group and one from the M group received atropine during operation and one patient from the C group received atropine in the first hour after the operation.

There were no significant differences between C and M groups in preoperative blood pressure. By comparing measures of blood pressure (regardless of analgesic type) taken before operation (po) and at admission to ICU (time point 0; see Figure 1), we found significant decrease in systolic pressure ($\Delta M_{SYS} = 19.4$ mmHg, $t(23) = 3.39$, $p = .003$), diastolic pressure ($\Delta M_{DIA} = 14.8$ mmHg, $t(23) = 5.08$, $p < .001$), and mean arterial pressure ($\Delta M_{MAP} = 16.3$ mmHg, $t(23) = 4.61$, $p < .001$).

When investigating the effect of analgesic on systolic blood pressure, diastolic blood pressure, mean arterial blood pressure, and heart rate we included body mass index and postoperative colloid intake as covariates in the model. Systolic blood pressure was significantly higher in the M group ($M_M = 115.9$ mmHg vs. $M_C = 104.4$ mmHg; $MSE = 1955.5$, $F(1,20) = 4.89$, $p = .04$). Comparable results were obtained for diastolic blood pressure

($M_M = 64.5$ mmHg vs. $M_C = 60.5$ mmHg; $MSE = 280.8$, $F(1,20) = 4.10$, $p = .05$) and mean arterial pressure ($M_M = 81.7$ mmHg vs. $M_C = 75.1$ mmHg; $MSE = 573.3$, $F(1,20) = 5.32$, $p = .03$) (Figure 1, 2, 3).

Due to the small sample size (and consequently low statistical power) and number of Bonferroni corrected pair-wise comparisons, none of the differences in each time point proved to be statistically significant. However,
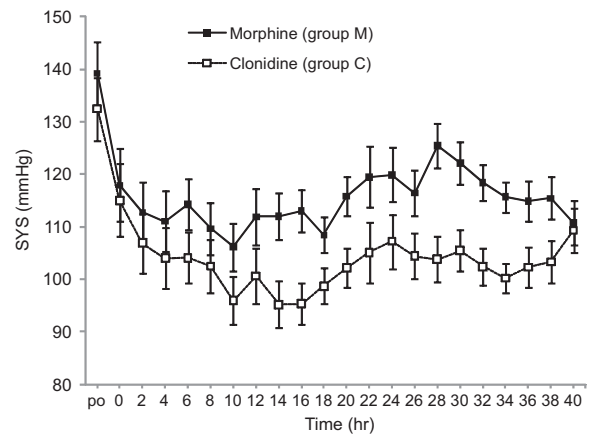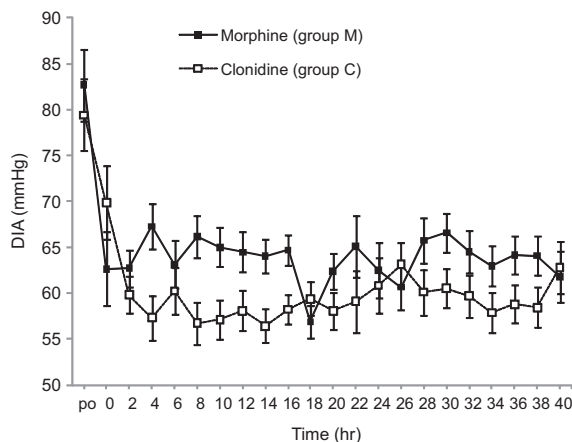

Figure 1. *Systolic blood pressure (SYS) during the study. Time point po denotes preoperative measurement and time 0 corresponds to measurement at admission to the intensive care unit. The patients in group M had statistically significant (p <.01) higher blood pressure than the patients in group C. The whiskerSYS ()srepresent standard error of the mean.*
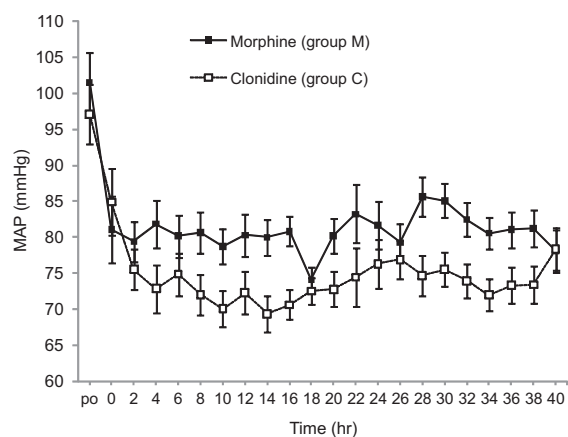
TABLE 1
Demographic, intraoperative and postoperative data.

	Morphine ($n = 12$)	Clonidine ($n = 12$)	Difference between groups
Age[a] (yr)	60.3 ± 6.3	59.0 ± 7.6	$t(22) = 0.47$, $p = .65$
Gender (female/male)	3/9	2/10	$\chi^2(1) = 0.25$, $p = .62$
BMI[a]	23.1 ± 5.4	28.0 ± 4.2	$t(22) = 2.49$, $p = .02$
ASA Physical Status			$\chi^2(1) = 0.38$, $p = .54$
2	10	11	
3	2	1	
Duration of anaesthesia[a] (min)	170.0 ± 49.6	157.9 ± 37.0	$t(22) = 0.68$, $p = .51$
Blood loss during op[a] (mL)	204.2 ± 113.7	166.7 ± 107.3	$t(22) = 0.83$, $p = .42$
Fluids[a] (intraoperative)			
Crystalloids (mL)	1500.0 ± 301.5	1416.7 ± 468.7	$t(22) = 0.52$, $p = .61$
Colloids (mL)	125.0 ± 226.1	333.3 ± 325.7	$t(22) = 1.82$, $p = .08$
Fluids[a] (in ICU)			
Crystalloids (mL)	3273.3 ± 570.5	3637.9 ± 506.1	$t(22) = 1.66$, $p = .11$
Colloids (mL)	93.8 ± 324.8	635.4 ± 481.1	$t(22) = 3.23$, $p < .01$
Per os (mL)	1870.8 ± 984.3	2476.7 ± 726.5	$t(22) = 1.72$, $p = .10$
Fluids[a] i.v. (in first 24 to 27 hours)			
Colloids + crystalloids (mL)	4177.1 ± 850.2	4916.7 ± 868.2	$t(22) = 2.11$, $p = .047$

[a] Arithmetic mean ± *SD*; BMI – body mass index; op – operation; ICU – intensive care unit; Fluids i.v. (in first 24–27 hours) – intravenous fluids given from the beginning of the operation until first 24 hours in ICU
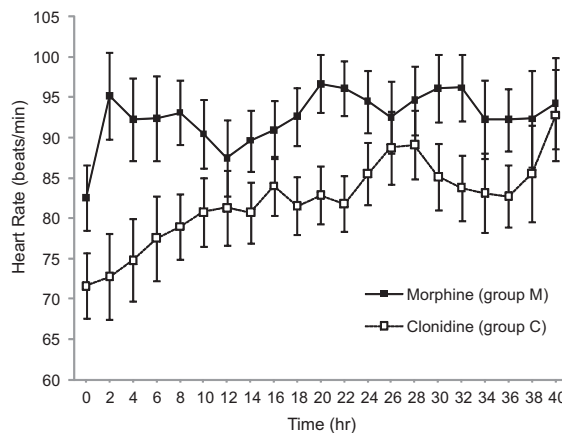
Figure 2. *Diastolic (DIA) blood pressure during the study. Time point po denotes preoperative measurement and time 0 corresponds to measurement at admission to the intensive care unit. The patients in group M had statistically significant (p <.05) higher diastolic blood pressure than the patients in group C. The whiskers represent standard error of the mean.*

Figure 4. *Mean heart rate of patients during the study. Time 0 corresponds to measurement at admission to the intensive care unit. The difference between Group M and group C was statistically significant only in the first 8 hours after admission to the intensive care unit (p <.05). The whiskers represent standard error of the mean.*

DISCUSSION

The results of this trial demonstrate a marked reduction in systolic, diastolic and mean arterial pressure throughout the early postoperative study period in C group. Patients received 300–460 µg of clonidine bolus according to their body weight (4 µg/kg) and from 15–23 µg/h of clonidine for postoperative period (0,2 µg/kg/h). Reduction in blood pressure is an expected effect of low dose α_2 adrenergic agonist clonidine *(3, 6)*. A similar survey of postoperative epidural clonidine found that clonidine of 20 µg/h while not 15 µg/h added to bupivacain and fentanyl enhances analgesia, but it also produces hemodynamic effects and increases the need for circulatory support with vasopressors *(7)*. However in that study EC was placed lower, at T9-12. It is known that with epidural clonidine a more profound hypotension occurs with higher thoracic epidural injection than with lower thoracic and lumbar levels *(8, 9)*.

Several surveys reported contradictory effects of epidural clonidine on hemodynamics. In some of them hypotension was reported while the others reported no hemodynamic adverse effects of clonidine *(10, 11, 12, 13)*. Many recent surveys with epidural clonidine focusing also on hemodynamic side effects were conducted on patients undergoing obstetric, abdominal or spinal surgery *(14, 15)*. However, we can not directly compare these studies with our since ether clonidine dose, site of epidural injection or patient population were different.

Because our study was coupled with a study of epidural clonidine effects on immune system we did not use any vasoactive or inotropic agents for treating hypotension, patients who needed such treatment were excluded from the study. For treating hypotension or bradycardia we used fluid load and atropine if needed. Therefore we can demonstrate that the C group received significantly more colloid fluids in early postoperative period.

Figure 3. *Mean arterial blood pressure (MAP) during the study. Time point po denotes preoperative measurement and time 0 corresponds to measurement at admission to the intensive care unit. The patients in group M had statistically significant (p <.001) higher blood pressure than the patients in group C. The whiskers represent standard error of the mean.*

the effect sizes were quite large for all analyzed blood pressure measures, i.e. Cohen's *d*s were larger than 0.5 in more than half of pair-wise comparisons.

Average heart rate in group M was higher than in group C throughout the study period, but this overall difference was not statistically significant ($M_M = 92.6$ beats/min vs. $M_C = 82.2$ beats/min; $MSE = 2268.0$, $F(1,20) = 3.29$, $p = .08$) (Figure 4). However, the difference was most prominent and statistically significant in the first 8 hours after admission to ICU ($M_M = 93.3$ beats/min vs. $M_C = 76.0$ beats/min; $MSE = 628.3$, $F(1,20) = 5.67$, $p = .03$), mostly due to a much quicker increase in heart rate of the M group patients (compared to a more gradual increase of heart rate in the C group).

Colloid fluids received during operation were not significantly higher in C group ($p =$.08), but the effect size was quite substantial (Cohen's $d = 0.53$). Patients in C group received significantly more i.v. fluids in first 24–27 h (from beginning of the surgery until 24 hours postoperatively) than those in M group (4177.1 mL ± 850.2 vs. 4916.7 mL ± 868.2). Large amounts of fluids (> 4 L) given in first 24 hours in patients after lung surgery is a recognized risk factor for developing ALI *(5, 16)*. Although none of the patients included in the study had any pulmonary complications, the patients in group C were according to fluids administered placed in a greater risk for developing ALI.

At the time of the survey, the standard policy of thoracic ward was to give 1.5 L of i.v. fluids on the day of operation and on the first postoperative day, plus more if needed for hemodynamic stability. The decision for additional fluids was made by the individual surgeon and was guided mainly by systolic blood pressure.

We concluded that epidural clonidine as an adjuvant to high thoracic epidural analgesia causes hypotension in patients undergoing lung surgery. Treating hypotension with fluid load might be hazardous, since large amounts of fluid in early postoperative period after lung surgery puts the patients in risk of developing ALI.

In this study we demonstrated a significantly lower heart rate in group C than in group M. Most prominent was the difference in the first 8 hours after the operation. This is a desired effect of clonidine, which is a known sympatholytic agent *(17)*. Clonidine reduces heart rate partly by a presynaptically mediated inhibition of norepinephrine release at the neuroreceptor junction and partly by vagomimetic effect *(3)*. In this way it can reduce myocardial oxygen demand. We recorded a bradycardic event with heart rate < 45 at 4 patients in group C (3 during the operation, 1 in ICU) and at 1 patient in group M (in ICU). In all cases bradycardia was promptly corrected with 0.5–1 mg of atropine.

We concluded that lower heart rate after the surgery caused by epidural clonidine is beneficial for patients and that any bradycardia can be easily corrected with atropine.

CONCLUSIONS

Although clonidine is recognized as a good adjuvant to epidural analgesia because of its analgesic and sympatholitic properties, the decision for its use for patients undergoing lung surgery must be made individually. Its effect of lowering the heart rate is beneficial for patients with heart diseases since in this way myocardial oxygen demand is reduced. But the side effect of clonidine used in high thoracic epidural injection is hypotension. Therefore we propose that epidural clonidine in this patients

can be used, but with conservative fluid regimen in early postoperative period. In this case, it's appropriate to use hemodynamic monitoring for better guidance in treating hypotension with vasoactive or inotropic drugs.

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