

Survival rate in patients after sudden cardiac arrest at the university hospital of northern Norway treated with or without opioids: A retrospective evaluation

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ABSTRACT

Background: Experimental studies both *in vivo* and *in vitro* show significantly increased survival rate in animals and in cortical neurons respectively exposed to acute hypoxia and pre-treated with opioids compared to non-treated counterparts. Thus, the main aim of the study was to examine survival rates in patients after sudden cardiac arrest (SCA) in the hospital who were or were not treated with opioids before and/or during cardiac pulmonary resuscitation (CPR). **Methods:** The registry SCA database at the University Hospital of Northern Norway (UNN) for the period of January 2006-December 2009 was used to obtain data for the evaluation. Inclusion criteria were observed SCA at UNN for patients with American Society of Anesthesiologists (ASA) 1-3. Exclusion criteria included ASA four to five patients and unobserved SCA. Study patients were divided into two groups: Those not treated with opioids and those treated with opioids not more than 3 h before and/or during CPR. Survival rate 1, 2, 3 and 28 days post CPR were compared for the two groups. **Results:** A total of 117 patients were registered in the SCA database at UNN for the period from January 2006 to December 2009. Sixty seven patients were excluded from the study: 17 patients had an unknown time of SCA début, two patients had only syncope and 48 were ASA four to five patients. A total of 50 ASA one to three patients were included in the study, 33 and 17 patients respectively in the control and opioid-treated groups. The patients who were treated with opioids before or during CPR had a significantly higher 1, 2, 3 and 28 days survival rate as compared to those receiving only conventional CPR. The model was adjusted for duration of CPR ($P=0.047$) and treatment with adrenaline ($P=0.779$) in the groups. Adjusted Odds ratio was 0.075 (95% confidence interval (CI): 0.015-0.387). Relative risk of fatal outcome in the opioids group was 0.2944 (95% CI: 0.1549-0.5594). **Conclusion:** Significantly higher 1, 2, 3 and 28 days survival rate and reduced duration of CPR were found in the patients additionally treated with opioids compared to ordinary resuscitation. Further prospective, randomized, controlled trials are needed to investigate the effects of early administration of opioids during CPR on survival and brain function in patients with witnessed in-hospital SCA.

Key words: Cardiac arrest, opioids, survival rate

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INTRODUCTION

Late one evening in October 2005, while on duty as a doctor-anesthesiologist I received an alarm about sudden

cardiac arrest (SCA) in the surgical department. Upon my arrival at the room, the patient had dilated pupils, absent carotid pulse and no respiratory effort. Electrocardiogram showed ventricular fibrillation (VF). Direct current biphasic shock of 200 J was delivered immediately and advanced cardiac pulmonary resuscitation (CPR) was started. The decision to discontinue resuscitation was taken after approximately 35 min of timed resuscitation when the patient was asystolic and pulseless with no respiratory effort. About 15 min after resuscitation had ceased the patient was found to be breathing. The patient was taken to the high dependency unit for respiratory and cardiac monitoring and the following morning she was conscious

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and alert with no detectable neurological defects. Later when reviewing this clinical situation I found that the patient had been treated with morphine 1 h before SCA. One previously published clinical case described full neurological recovery in a young man who overdosed on opioids and who regained sinus rhythm many minutes after resuscitation had been abandoned.^[1] Moreover, in experimental studies with mice and rats exposed to acute hypoxia, morphine has been shown to improve the survival rate^[2,3] significantly. In addition, cell culture studies indicate that both endogenous and exogenous opioids can protect cortical neurons from hypoxia-induced cell death and induce ischemic tolerance in cerebellar Purkinje cells, which have been subjected to ischemia-reperfusion conditions.^[4-6] Opioid receptor agonists had been shown to increase tissue preservation and survival time of organs before their use in transplantation surgery and increase survival time during severe and acute hypoxia.^[7-9]

Thus, the aim of the retrospective evaluation was to determine survival rate in patients after SCA, who were or were not treated with opioids before and/or during CPR.

METHODS

This study was reviewed and approved by the chief of the regional ethical committee.

Study design and settings

The data for the retrospective study was obtained from the Registry of Cardiopulmonary Resuscitation of SCA at University Hospital of Northern Norway (UNN) for the period from January 2006 to December 2009. The sample size was not planned.

Subjects

Adult patients (over 18 years) who experienced cardiac arrest and resuscitation in UNN and were registered in the database of SCA.

Inclusion criteria

ASA one to three patients with witnessed SCA.

Exclusion criteria

ASA four to five patients, age less than 18 years and unwitnessed SCA.

The ASA (American Society of Anesthesiologists) physical status classification: ASA 1: A normal healthy patient. ASA 2: A patient with a mild systemic disease such as mild diabetes, controlled hypertension, obesity. ASA 3: A patient with a severe systemic disease that is not incapacitating such as angina, chronic obstructive pulmonary disease, prior myocardial infarction. ASA 4: A patient with an incapacitating

disease that is a constant threat to life such as chronic heart failure, renal failure etc., ASA 5: A moribund patient not expected to survive 24 h, such as ruptured aneurysm.

Assignment

Patients included in the study were allocated to two groups: Those who were not treated with opioids or were treated not more than 3 h before and/or during CPR. Assessment: 1, 2, 3 and 28 days survival after CPR.

Statistical analysis

The data were entered in Microsoft Excel 2002 for Windows (Microsoft Office, Microsoft Corp, 1985-2001) and then transferred to MedCalc[®] for Windows, version 7.2.1.0. The normality of the data distribution was assessed by the Kolmogorov-Smirnov test. Unpaired Student's *t*-test was used for comparison of means for age and duration of CPR. Fisher's exact test was used to test differences in survival and other categorical variables. The data was also transferred to SPSS 16.0 for Windows (SPSS, Inc., Chicago, Ill) for multivariate-adjusted logistic regression analysis. The model was adjusted for duration of CPR and treatment with adrenaline. Adjusted odds ratios (ORs), relative risk of fatal outcome and 95% confidence intervals (CIs) for treatment with opioids were determined. A *P* < 0.05 was regarded as statistically significant.

RESULTS

A total of 117 patients with hospital cardiac arrest alarm were registered in the SCA database at UNN for the period from January 2006 to December 2009.

Sixty seven patients were excluded from the study: 17 patients had unknown time of SCA debut, two patients who had only syncope and 48 were ASA 4-5 with terminal stadium of oncology, chronic heart failure, renal failure etc.

Fifty ASA one to three patients were included in the study. All had observed SCA and basic resuscitation was started immediately by medical staff trained in CPR.

Seventeen patients received treatment with opioids [Table 1]. Of these nine patients were treated with Morphine 1-10 mg i.v., mean (\pm SD): 4.33 \pm 3.37 mg before or during CPR. Seven patients received Fentanyl 50-200 mcg i.v., mean (\pm SD): 135.7 \pm 55.6 mcg. One patient was treated with Paralgin Forte 400 mg po before SCA.

Table 2 summarizes characteristics, physical status by ASA classification and diagnoses of all included patients. The patients in both groups were not significantly different in demographic and clinical characteristics such as age, gender, physical status by ASA classification and diagnose.

Table 1: Diagnose and dose of opioids

Patients	Diagnose	Opioids
1	AMI	Morphine 3 mg i.v. before SCA
2	Cancer in pancreas, liver insufficiency	Paralgin Forte 400 mg po before SCA (codeine 30 mg where of 5-15% this dose converts to Morphine)
3	By pass operated	Fentanyl 150 mcg i.v. during CPR
4	AMI	Morphine 2.5 mg i.v. before SCA
5	AMI	Morphine 2.5 mg i.v. before SCA
6	Sepsis/ARDS	Fentanyl 200 mcg i.v. during CPR
7	Sepsis/ARDS	Fentanyl 150 mcg i.v. during CPR
8	AMI	Morphine 5 mg i.v. during CPR
9	AMI	Fentanyl 100 mcg i.v. during CPR
10	AMI	Morphine 1.0 mg i.v. before SCA
11	AMI	Morphine 2.5 mg i.v. before SCA
12	AMI	Morphine 10 mg i.v. before SCA
13	Sepsis	Fentanyl 50 mcg i.v. during CPR
14	Pneumonia	Fentanyl 100 mcg i.v. during CPR
15	AMI	Morphine 10 mg i.v. before SCA
16	Trauma	Fentanyl 200 mcg i.v. during CPR
17	AMI	Morphine 2.5 mg i.v. before SCA

AMI – Acute myocardial infarction; ARDS – Acute respiratory distress syndrome; SCA – Sudden cardiac arrest; CPR – Cardiac pulmonary resuscitation; i.v. – Intravenous

Table 2: Demographic characteristics, physical status by ASA classification and diagnoses of the patients

Variable	Control (n=33) (%)	Opioids (n=17) (%)	P value
Age±SE	68.4±2.39	66.5±3.78	0.65
Gender M/W	16/17	11/6	0.37
ASA 2 n	12 (36.3)	3 (17.6)	0.2
ASA 3 n	21 (63.6)	14 (82.3)	0.2
Diagnose			
AMI, n	21 (63.8)	10 (58.8)	0.76
Sepsis/ARDS n	2 (6)	3 (17.6)	0.32
Pneumonia n	2 (6)	1 (5.8)	-
By pass operated n	2 (6)	1 (5.8)	-
AF/DM n (%)	1 (3)	0	-
Allergic reaction	1 (3)	0	-
Cold n	1 (3)	0	-
Lung emboli n	1 (3)	0	-
Cancer rectum/operated n	1 (3)	0	-
Cancer in pancreas, liver	0	1 (5.8)	-
Insufficiency n			
Trauma n	0	1 (5.8)	-
Schizophrenia n	1 (3)	0	-

ASA – American Society of Anesthesiologists; AMI – Acute myocardial infarction; ARDS – Acute respiratory distress syndrome; M – Men; W – Women

Type of heart rhythm registered at the moment of cardiac arrest, treatment during CPR and 1, 2, 3 and 28 days survivals are listed in Table 3. There were no significant differences in the heart rhythm registered at the moment of cardiac arrest and in the treatment during CPR between these groups. However, the patients treated additionally

with opioids demonstrated significantly higher 1, 2, 3 and 28 days survival rate as well as reduced duration of CPR compared to those who received only conventional resuscitation.

Finally, the multivariate-adjusted logistic regression analysis found a significant influence of CPR duration (adjusted ORs=0.075, 95% CI=0.015-0.387, $P=0.047$) and not significant influence of treatment with adrenaline ($P=0.779$) on survival at the end of CPR. Relative risk of fatal outcome in the opioids group was 0.2944 (95% CI: 0.1549-0.5594).

DISCUSSION

Recently published results from the large prospective, observational study in the USA have demonstrated that 1st day survival after in-hospital cardiac arrest was approximately 50% for all patients with documented cardiac rhythms (VF/ventricular tachycardia, pulseless electrical activity and asystole) with further significant reduction in survival rate at discharge from hospital to 25% from all resuscitated patients.^[10] Another recent study of in-hospital cardiac arrest has found that only 35% of all patients were alive at the end of CPR and ultimately only 11% of all resuscitated patients were discharged alive from the hospital.^[11] Consistent with the data from the USA study, in the control group of the present study 1st day survival was 45.4% of all resuscitated patients, which then decreased to 24.2% at the 28th day after SCA [Table 3]. In sharp contrast, for the patients additionally treated with opioids, 1st day survival was 88.2% which then only decreased to 82.3% at the 28th day after SCA [Table 3]. It is unclear why the survival rate after in-hospital cardiac arrest and ordinary CPR decreases so significantly in the time interval up to discharge from hospital. In contrast, survival rate in the opioid treated group showed very little decrease in the same time period.

Current evidence in neurobiology demonstrates that acute hypoxia-induced uncontrolled release of glutamate and the consequent stimulation of NMDA receptors results in excessive Ca^{2+} influx, which finally leads to the total depolarisation of neurons.^[12-15] Furthermore, excessive intracellular Ca^{2+} accumulation activates enzymes including proteases, lipases and endonucleases with subsequent damage to cellular lipids, proteins and DNA which lead to free radical production, membrane lipid breakdown and proteolysis.^[12-15] Finally, Ca^{2+} intracellular overloading leads to increased mitochondrial and cellular permeability with following neuronal swelling, nuclear pyknosis, acidophilic cytoplasm and cell lysis.^[16] Anesthetics such as volatile agents, barbiturates and propofol with their ability to antagonize glutamate-mediated excitotoxicity are logical candidates

Table 3: Type of heart rhythm registered at the moment of cardiac arrest, treatment during CPR and 1, 2, 3, 28 days survival rate

Variable	Control (n=33) (%)	Opioids (n=17) (%)	P value
Heart rhythm registered			
PEA n, (%)	5 (15.5)	3 (17.6)	1.00
VF n, (%)	19 (57.7)	8 (47)	0.55
Asystole n, (%)	9 (27.7)	6 (35.2)	0.74
Treatment during CPR			
Adrenalin n, (%)	27 (81.8)	13 (76.4)	0.71
Atropine n, (%)	18 (54.5)	6 (35.2)	0.24
DC shock n, (%)	17 (51.5)	10 (58.8)	0.76
Intubation of trachea n, (%)	16 (48.4)	11 (64.7)	0.37
Antiarrhythmic treatment n, (%)	8 (24.2)	6 (35.2)	0.51
Bicarbonat n, (%)	6 (18.1)	2 (11.7)	0.69
Duration of CPR (min)	21.9±3.8	11.7±2.3	0.062
1 day survival n, (%)	15 (45.4)	15 (88.2)	0.005
2 day survival n, (%)	13 (39.3)	15 (88.2)	0.001
3 day survival n, (%)	12 (36.3)	15 (88.2)	0.0007
28 day survival n, (%)	8 (24.2)	14 (82.3)	0.0001

PEA – Pulseless electric activity; VF – Ventricular fibrillation; CPR – Cardiac pulmonary resuscitation; DC – Direct current

for neuroprotection during acute hypoxia.^[17] However, as far as I am aware there are no published clinical trials with anesthetics used for neuroprotection during CPR. The ability of anesthetics to produce vasodilatation and therefore to reduce significantly perfusing blood pressure was possibly a main argument against the idea of trying them during early CPR. To my knowledge there are also no published clinical trials with opioids for neuroprotection during CPR. Thus, the present study appears to represent the first attempt to evaluate the effect of intravenous opioid administration on short-term survival in patients after in-hospital cardiac arrest and CPR. However, opioids have been well studied in different experimental model of ischemia and acute hypoxia.^[2-9,18] Recently published experimental studies demonstrated that opioids can preserve cellular status during acute hypoxia in many experimental model systems including the intestine,^[19] skeletal muscle,^[20] the myocardium^[21,22] and the CNS.^[23] The partial mu opiate agonist buprenorphine was demonstrated to protect a sub-population of thalamic reticular neurons 45 min after resuscitation following cardiac arrest in rats.^[24] Morphine has been found to protect neocortical neurons from glutamate-induced excitotoxic injury via delta-opioid receptors in cortical neurons.^[4] Another study in rats demonstrated that morphine protects the primary neonatal astrocytes from glutamate toxicity via modulation of intracellular redox status.^[25] On the other hand, application of naloxone (antagonist to opioid receptors) in rats resulted to 100% mortality during acute hypoxia while 90% of morphine treated animals survived after 70 min of exposition to acute hypoxia.^[2] Moreover, several clinical case reports have raised the question as to

whether the use of naloxone could be a cause of SCA and death in patients with oxygenation problems.^[26-28] In fact, opioids are generally accepted for treatment of patients with SCA due to acute myocardial infarction and I was unable to find any published clinical trials with opioids observed to increase mortality. Moreover, the present study demonstrates that use of opioids during CPR did not increase risk of fatal outcome.

In the present study, the patients in both groups were very similar in demographic, clinical characteristics and standard treatment during CPR but duration of resuscitation of the patients in the control group was almost 2 times longer than for those who were given opioids. Indeed, the factor (duration of CPR) alone can be an independent predictor for poor outcome after SCA^[11] and therefore may be considered as a limitation factor of the study.

Recently, adrenalin was demonstrated as an independent predictor of poor outcome in a large retrospective registry study.^[29] However, the present study did not find any significant influence of treatment with adrenaline ($P=0.779$) on survival at the end of CPR.

Finally, the patients additionally treated with opioids before/or during CPR demonstrated significantly higher 1, 2, 3 and 28 days survival rate and reduced duration of CPR compare to the patients with ordinary resuscitation. Further clinical trials are needed to investigate the effects of early administration of opioids during CPR on survival and brain function in patients with witnessed in-hospital SCA.

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