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Sparv, David; Bhiladvala, Pallonji; Van Dijkman, Anna; Harnek, Jan; Madsen-Härdig, Bjarne; Björk, Jonas; Ekelund, Ulf; Erlinge, David

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PO Box 117
221 00 Lund
+46 46-222 00 00

The analgesic effect of oxygen during percutaneous coronary intervention (The OXYPAIN Trial)

David Zughaft^{1,2}; Pallonji Bhiladvala^{1,3}; Anna van Dijkman^{1,3}; Jan Harnek^{1, 2}; Bjarne Madsen Hardig¹; Jonas Bjork⁴; Ulf Ekelund⁵ and David Erlinge.^{1, 2}.

¹Department of Cardiology, Lund University, Sweden

²Department of Coronary Heart Disease, Skane University Hospital, Lund, Sweden

³Department of Coronary Heart Disease, Skane University Hospital, Malmö, Sweden

⁴R&D centre Skane, Skane University Hospital, Lund, Sweden

⁵Department of Clinical Sciences, Lund University, Sweden

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CORRESPONDING AUTHOR:

David Erlinge

Department of Cardiology, Lund University

Skane University Hospital

SE-221 85 Lund, Sweden

Fax: +46 46 15 78 57 Tel: +46 46 17 2597

E-mail: david.erlinge@med.lu.se

ABSTRACT

Introduction: Oxygen is considered to have analgesic effects, but the evidence is weak. Oxygen may be harmful to the ischemic myocardium. The aim was to investigate the analgesic effect of oxygen during percutaneous coronary intervention (PCI) and to evaluate cardiac injury.

Material and methods: The OXYPAIN was a phase II randomized trial with a double blind design. 305 patients were randomized to receive oxygen or atmospheric air during PCI. The patients were asked to score chest pain by the Visual-Analog Scale (VAS). The use of analgesic agents and troponin-t was measured.

Results: There was no significant difference in pain between the groups: Oxygen: 2.0, [2.0-4.0], Air: 2.0, [2.0-5.0] (median, interquartile range 25-75%, $p=0.12$). The median difference in score of VAS was [95% CI]: 0, [0-1.0]. The oxygen group received 0.44 ± 0.11 mg of morphine versus 0.46 ± 0.13 , $p=n.s.$ The peak value of troponin-t post-PCI was 38, [11-352] nmol/ml in the oxygen group and 61, [16-241] for patients treated with air, $p = 0.46$.

Conclusions: The use of oxygen during PCI did not demonstrate any analgesic effect. There was no difference in myocardial injury measured with troponin-t or in the morphine dose. Our results do not support routine use of oxygen. (NCT01413841).

KEYWORDS

Ischemic pain, oxygen therapy, percutaneous coronary intervention,

INTRODUCTION

The use of oxygen is a cornerstone in cardiovascular medicine and has been routinely administered for a wide range of symptoms such as hypoxia, shortness of breath, chest pain, nausea and anxiety(1). Oxygen therapy is indisputable when a patient suffers from hypoxia, defined as a partial oxygen pressure (pO_2) <8 kPa, or measured by pulse oxymetry (SpO_2) $< 90\%$ (2, 3) and a sufficient oxygenation is vital for all bodily tissues (4, 5). American and European guidelines (ACC, AHA, ESC) states a Class Ia recommendation for oxygen therapy in patients with an $SpO_2 < 90\%$ ($pO_2 < 60$ mmHg = 8,0 kPa), and a Class IIa recommendation for oxygen administration to all patients diagnosed with an acute coronary syndrome (ACS) including ST Elevation Myocardial Infarction (STEMI) upon the first 6 hours after symptoms onset(6-8).

However, even though oxygen therapy is vital for the hypoxic patient, evidence for other indications is poor and mostly based on non-randomized studies, preclinical trials and clinical experience. No larger randomized trials have been able to demonstrate that oxygen reduces ischemic symptoms, shortness of breath, nausea or anxiety(9). Despite lack of evidence, almost 90% of patients presenting with acute coronary syndrome is provided with oxygen, regardless levels of SpO_2 (2).

Ischemic cardiac pain occurs when the heart muscle is insufficiently oxygenated either due to decreased coronary blood flow or increased oxygen consumption, and is one of the most common symptoms of ACS and STEMI(10). During a PCI, ischemic pain is common due to temporary interference of coronary blood flow(11). In order to treat this pain, standard hospital guidelines recommend analgesic medication (nitrates and morphine) and oxygen therapy (2, 12). Ischemic pain is not easily assessed since it represents a subjective, individual experience of every patient(13). One of the few evidence based tools for pain assessment is the Visual-Analogue Scale (VAS) (14, 15).

The theory behind using oxygen in the treatment of coronary heart disease, suggests that oxygen therapy may reduce ischemic symptoms such as chest pain, and in addition, decrease the size of the

myocardial infarction and reduce morbidity and mortality(16). However, increasing levels of oxygen in the blood may cause a coronary vasoconstriction and by that a reduction of coronary blood flow (CFR) and cardiac output (CO), as well as an increased mean arterial blood pressure (MAP), systemic vascular resistance (SVR) and levels of lactate in the blood(17-21) Recent publications suggest that this hemodynamic response may be harmful for the myocardium and even aggravate the ischemia(1, 9).

The aim of the OXYPAIN trial was thus to investigate the analgesic effect of oxygen during PCI and to study the peak value of the cardiac injury biomarker troponin-t, as a marker for infarct size. Our hypothesis was that the use of oxygen should decrease ischemic chest pain measured by the Visual Analogue Scale, and reduce the peak value of the troponin-t. However, the results did not support the hypothesis.

MATERIALS AND METHODS

Design

The OXYPAIN was a phase II randomized trial with a prospective, double blind design (ClinicalTrials.gov: NCT01413841), performed at two high-volume PCI-centers in Sweden. Patients were considered eligible for inclusion and randomization if the following inclusion criteria were fulfilled: Clinical evidence of stable angina or acute coronary syndrome, ≥ 18 years of age, angiographic significant stenosis eligible for PCI according to ESC guidelines(8), an oxygen saturation $\geq 95\%$ and signed informed consent. Key exclusion criteria were patients presenting with STEMI, hypoxia defined as oxygen saturation $< 95\%$, confusion and/or inability to comprehend the study information.

Procedure

Following randomization, the patients were provided with oxygen or atmospheric air by a nasal cannula at a flow rate of 3 liters/min. The oxygen saturation was measured continuously using the Philips Intellivue® Cardiac system, version M8010A (Royal Philips Electronics, Amsterdam, The Netherlands). **All patients received an intravenous injection of 2.5 mg Diazepam upon arrival at cathlab. Following insertion of an arterial sheath, 70 U/kg Heparin and 0.2 mg Nitroglycerin was injected. The patients were unaware during the procedure whether oxygen or atmospheric air was administered and if ischemic pain occurred, 2.5 mg of Morphine was administered. If the pain did not diminish, the Morphine dose was repeated.**

If SpO₂ subsided to a permanent level of < 95% during the procedure, the patients were excluded and treated according to standard hospital guidelines. **During balloon inflation and stent placement, the number of inflations was calculated (Table 2). Inflation time was 15-30 seconds, and the lesion complexity were categorized “A, B1, B2 and C” according to the ACC standard (Table 2). (23). After accomplished PCI, defined as 1 minute after removal of guiding catheter, the patients were asked by an investigator blinded to treatment to score maximum chest pain by a scale 0-10 (VAS) where 0 was translated to “no pain” and 10 to “worst conceivable pain”. The cardiac injury biomarker troponin-t was measured in the ACS cohort before and one day after the procedure prior to discharge. In the cohort of stable angina, troponin-t was measured only the day after PCI. The amount of analgesic agents was noted in the case report form. **Medical treatment was similar between groups (Table 3).****

Study endpoints

The primary endpoint of the trial was to investigate the possible analgesic effect, using VAS, of oxygen therapy during PCI in patients with stable angina or acute coronary syndrome. Secondary

endpoint was to determine if oxygen administration during PCI implies a reduction in levels of the troponin-t and to evaluate the quantity of analgesic agents administered.

Ethical aspects

The study was formally approved by the ethical review board of Lund, Sweden (DNR 114/11) and all patients enrolled in the study signed a written informed consent.

Sample size and statistical analysis

The statistical analysis was performed using the 5.0 version of the Graphpad Prism®. In the power calculation when planning the study we assumed that a reduction of pain with 30% was clinically meaningful. Based on previous VAS data from our coronary cathlab, a sample size of 150 in each group has an 80% power to detect a 30% difference between groups with a significance level (alpha) of 0.05 (two-tailed). Continuous variables of VAS, levels of troponin-t and use of the analgesic agent was calculated and reported as a mean $\pm$ standard deviation (SD), but also as median (interquartile range) if asymmetrically distributed. The interference between the groups of oxygen and air was based on the computation of 95% Confidence Interval Analysis and on either t-test or the Mann-Whitney U-test (Wilcoxon rank-sum-test) to determine statistical significance. A p-value of <0.05 was considered statistically significant. An explorative subgroup analysis of the main cohort was performed in the terms of stable angina versus ACS, and male versus female population.

RESULTS

A total of 305 patients treated by PCI were included and randomized in the OXYPAIN trial. All included patients were painless at randomization and had a SpO₂ of $\geq 95\%$. Five patients were excluded due to hypoxia during the procedure, leaving 154 patients in the oxygen group and 146 in the group of atmospheric air (Table 1). No adverse events (bleeding, stroke, periprocedural

infarctions or death) occurred during the procedures. At a 1 year follow up, adverse events was reported in 6,3% of the cases in the oxygen group and 4,2% in the group of atmospheric air (ns). The most common event was instant restenosis. In the result synthesis, the study did not result in any significant difference in occurrence of ischemic chest pain between the groups measured by the VAS score. There was no difference in the main cohort (Figure 1) or in the explorative subgroup analysis of stable angina (Figure 2a), ACS (Figure 2b), male (Figure 3a) and female (Figure 3b).

Main cohort, VAS

The oxygen group stated a VAS-score of 2.0, [0-4] versus the group receiving atmospheric air: 2.0, [0-5] (median, [interquartile range 25-75%]), $p = 0.12$ (Figure 1). The median difference in score of VAS was [95% CI]: 0, [0-1].

Stable angina and ACS, VAS.

In the subgroup of stable angina, the oxygen group stated a VAS-score of 2.0, [0-4] versus the air group: 2.0, [0-5] (median, [interquartile range 25-75%]), $p = \text{n.s.}$ (Figure 2a). In the corresponding values for the subgroup of ACS, the oxygen group stated a VAS-score of 2.0, [0-4] versus the air group: 2.0, [0-5] (median, [interquartile range 25-75%]), $p = \text{n.s.}$ (Figure 2b).

Male and female, VAS.

In the subgroup of male, the oxygen group stated a VAS-score of 2.0, [0-4] versus the air group: 2.0, [0-5] (median, [interquartile range 25-75%]), $p = \text{n.s.}$ (Figure 3a). In the subgroup of female, the oxygen group stated a VAS-score of 2.0, [0-5] versus the air group: 2.0, [0-5] (median, [interquartile range 25-75%]), $p = \text{n.s.}$ (Figure 3b).

Morphine administration.

In terms of analgesic agents, 14 /154 patients (9,1%,) received opiates in the oxygen group versus 17/146 patients (11,6%) in the group of atmospheric air (p= n.s.) The quantity of morphine administered was 0.44 ± 0.11 mg in the oxygen group versus 0.46 ± 0.13 (mean $\pm$ SD, p = n.s).

Myocardial injury measured with troponin-t.

The cardiac injury biomarker troponin-t was calculated in terms of peak value for the individual patient, where the peak value of troponin-t post-PCI was 38 , [11-352] nmol/ml in the oxygen group and 61, [16-241] nmol/l for patients treated with atmospheric air (median, interquartile range 25-75%), p = 0.46, Figure 4) . Median troponin difference between the groups were: 4 nmol/l (95% CI -8 till +17), indicating no clinically meaningful difference in troponin levels post-PCI.

Comparison of peak value regarding difference in pre and post values for the ACS patients did not differ between the groups.

DISCUSSION

The use of oxygen in patients during PCI did not demonstrate any significant analgesic effect or any reduction of opiate administration. Oxygen did not reduce myocardial injury as measured with troponin-t.

The use of oxygen for patients with hypoxia is indisputable (2, 3). However, hypoxia only occurred in 5 out of 305 patients during PCI, leaving 98% of the patients with normal saturation. Thus, hypoxia in patients with stable angina or ACS does not seem to be a major concern, and with the present finding

that oxygen does not provide any significant relief of pain, the routine use of oxygen during PCI could be questioned.

The amount of pain medication did not differ between patients treated with oxygen or air. Conclusions about the relevance of the analgesic doses should be drawn by caution, since only 15% of the main cohort received any pain medication, and the doses were relatively low. This finding is in consistent with other publication where the correlation between analgesic doses and VAS was poor(24) (25) However, the findings support the result that oxygen does not decrease the occurrence of ischemic chest pain during PCI.

Troponin-t

As a secondary finding, the OXYPAIN trial could not show any effect of oxygen treatment on peak value of the cardiac injury biomarker troponin-t, as a marker of myocardial injury. However, troponin-t is highly sensitive(26) and we observed a wide range of peak values in the study. Exploratory analyses of net increase (troponin after PCI – troponin before PCI) were also negative. In conclusion, our results do not provide evidence for reduction of infarct size by the use of oxygen during PCI.

Limitation of the study

Occurrence of chest pain during PCI in the main cohort was relatively rare, and between 30-40% of all patients scored their individually experience of pain to 0 at the VAS-scale, indicating no pain. It is possible that it would have been easier to detect an analgesic effect in a population more affected by pain. The study did not result in any significant result of difference, implying that it could be underpowered. However, it demonstrates with a 95% confidence interval that the difference is not larger than 1 point of VAS in the main cohort, which demonstrates that oxygen therapy has no clinically relevant effect. Experience of pain is one of the most subjective impressions for the patient

and is difficult to assess for the health care professionals(27). When evaluated in earlier publications, the VAS score differs regarding gender and age, and may be related to how the instruction of use is provided(28). Even though the VAS-scale has limitations, it is one of the few evidence bases pain assessment tools. (14)

The patients in the OXYPAIN trial received oxygen by a nasal cannula. We did not measure pO₂-levels during the procedure, why a possible objection could be if the oxygen dose was appropriate for analgesic effect. However, no trials have been able to demonstrate what doses of oxygen that would be required for a clinical effect. In addition, oxygen administration at a flow rate of 3 l/min is currently a standard dose for pain management. The SpO₂-level was measured continuously during the PCI, so we do know that all patients were kept at a SpO₂ $\geq$ 95%.

CONCLUSION

The use of oxygen instead of atmospheric air in patients treated by PCI did not result in any significant analgesic effect. The study could be underpowered, but it shows with 95% confidence interval that the difference is not larger than 1 point in VAS in the main cohort. There was no difference in myocardial injury as measured with troponin t. Our results do not support routine use of oxygen for pain relief during PCI for patients with normal oxygen saturation. A positive aspect is that we did not see any indication of doing harm to the patients by giving oxygen. The results of the OXYPAIN are intriguing considering the widespread use of oxygen during PCI in patients with normal saturation. A larger randomized multicenter trial would be required to firmly determine whether oxygen in patients with coronary heart disease treated with PCI with normal oxygenation have effects on pain, morbidity or mortality.

DECLARATION OF INTEREST

The authors report no conflicts of interest

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