A Retrospective Study of the Effects of Iloprost Infusion on Peripheral Arterial Oxygen Saturation in Patients with Critical Limb Ischemia

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Abstract

Purpose: To determine the usefulness of pulse oximetry in patients receiving iloprost infusion for treatment of critical limb ischemia unsuitable for revascularization.

Material and methods: A total of 42 patients [28 male, mean age 61.80±5.81 years] were included. Patients were those who considered as unsuitable for revascularization based on angiographic study and received single-dose infusion of iloprost at 2.0 ng/kg/min for 8 hours daily. The treatment was planned to last for about two weeks. Ankle brachial index values and peripheral arterial oxygen saturation values using pulse oximetry were obtained before and after the treatment.

Results: Treatment was complete in 42 patients. A total of 23 patients [54.7%] had pain relief and 15 patients [35.7%] had improvement in walking. Percentage changes in ankle brachial index and peripheral arterial oxygen saturation values were not significantly correlated [r=0.229, p=0.15]. Both ankle brachial index and peripheral arterial oxygen saturation values showed significant improvement after completion of the treatment. Percentage change in peripheral arterial oxygen saturation showed significant correlation with pain relief [r=0.449, p=0.003] whereas showed no correlation with improvement in walking [r=0.298, p=0.053].

Conclusion: Iloprost infusion seems promising in patients with critical limb ischemia and its use is associated with better oxygen delivery to the ischemic lower extremity tissue, which might be easily assessed using pulse oximetry.

ABBREVIATIONS

CLI: Critical Limb Ischemia, PAOD: Peripheral Artery Occlusive Disease, ABI: Ankle Brachial Index, SpO2: Peripheral Oxygen Saturation Measured by Pulse Oximetry, VAS: Visual Analog Scale

INTRODUCTION

Critical limb ischemia [CLI] has been defined as the advanced stage of peripheral artery occlusive disease [PAOD] and characterized by severe walking disability, trophic skin changes and tissue loss. Its incidence was reported to be ranging from 113 to 200 cases per 100,000 populations. Although revascularization rates increased up to 70% in patients with CLI, it was reported that about 20% of patients are being considered as unsuitable candidates for revascularization and medical therapy is the only chance to prevent amputation [1].

Iloprost is the synthetic analogue of prostacyclin and its therapeutic benefit in treatment of PAOD has been demonstrated in earlier pharmacological studies [2]. More recently iloprost treatment was shown to increase circulating endothelial progenitor cells in patients with CLI [3]. In clinical side, iloprost treatment was shown to promote healing of skin ulcers in patients with advanced PAOD [4].
Ankle brachial index [ABI] measurement is the most commonly used tool for assessment of peripheral flow in diagnosis and follow-up of patients with PAOD. However data is limited regarding its reliability and usefulness in patients with advanced stage PAOD who receive medical therapy [5,6]. Some studies reported that peripheral arterial oxygen saturation that is measured using a pulse oximetry probe [SpO₂] showed comparable accuracy to ABI measurement in diagnosis of PAOD [7]. However, to our knowledge, there has been no study reporting its use specifically in assessment of peripheral arterial oxygenation in CLI patients receiving iloprost treatment.

In this study we report our institutional results regarding the use of ABI and pulse oximetry in CLI patients who were considered as unsuitable candidates for any revascularization procedure and received a two-week protocol of iloprost infusion.

MATERIAL AND METHODS

The study was approved by local ethics committee [2013/83116987-407]. A procedural informed consent was obtained from each patient. This retrospective cohort study was conducted in a tertiary university hospital and made up of patients who received iloprost infusion therapy between May 2013 and December 2013. Search of the hospital database revealed that a total of 78 patients received iloprost infusion therapy between the dates given. Among these, eligible patients were those having symptoms of CLI more than two weeks with an ankle systolic pressure <50 mmHg [8] with peripheral arterial stenosis or occlusion being visualized in angiographic study and those who were considered as unsuitable candidates for surgical or endovascular revascularization due to presence of various conditions including poor distal vascular bed [25 patients], failed previous grafts or stents [3 patients] and high risk of operative failure [14 patients [8 patients had advanced chronic obstructive pulmonary disease, 2 patients had previous abdominal surgery and 2 patients had recent cerebral infarction]]. Patients with recent acute myocardial infarction, heart failure [NYHA=II], electrocardiogram findings of ventricular arrhythmia, severe hypertension, active phase peptic ulcer, low platelet counts, end-stage renal failure, severe hepatic failure, poor diabetes control, previous history of cerebrovascular disease and coagulation disorder were not included. Study group was comprised of a total of 42 patients [28 male, mean age 61.3±9.7 years]. Patients’ baseline characteristics of patients (n=42).

Baseline characteristics of patients (n=42).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients n=42</th>
</tr>
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<tbody>
<tr>
<td>Males (%)</td>
<td>28 (%66.7)</td>
</tr>
<tr>
<td>Age, years</td>
<td>61.80±5.81</td>
</tr>
<tr>
<td>Diabetes</td>
<td>22 (52.4%)</td>
</tr>
<tr>
<td>Tobacco use at the time of treatment</td>
<td>21 (50.0%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>18 (42.9%)</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>9 (21.4%)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>16 (38.1%)</td>
</tr>
<tr>
<td>Previous revascularization</td>
<td>19 (45.2%)</td>
</tr>
</tbody>
</table>

deterioration in signs and symptoms of CLI during hospital stay. A total of 23 patients [54.7%] had pain relief and 15 patients [35.7%] had improvement in walking ability.

ABI values and SpO2 values that were obtained before and after the treatment were given in Table 2. Percentage changes in ABI and SpO2 values were not significantly correlated [ρ=0.229, \( p=0.15 \)]. Both ABI [\( p<0.001 \)] and SpO2 [\( p<0.001 \)] showed significant improvement after completion of the treatment [Table 2]. Percentage change in ABI values showed no correlation with improvement in walking ability [\( r=0.174, p=0.269 \)] and pain relief [\( r=0.115, p=0.467 \)]. Percentage change in SpO2 values showed significant correlation with pain relief [\( r=0.449, p=0.003 \)] whereas showed no correlation with improvement in walking ability [\( r=0.298, p=0.053 \)] (Table 3).

A post-hoc power analysis was performed based on a medium population effect size of 0.5 [10,11]. The sample size in this study [n=40] achieved 95.3% power for the non-significant correlation observed in percentage changes between SpO2 and ABI values with an α significance level of 0.05.

**DISCUSSION**

Main result of the study was that lower extremity peripheral arterial oxygen saturation showed significant improvement after completion of a two-week protocol of iloprost infusion and the increase observed in tissue oxygenation was of clinical importance since pain relief was significantly and positively correlated with time-dependent changes in SpO2 values whereas such correlation was not present in regard to ABI values. Both ABI and SpO2 values showed significant changes in paired comparisons indicating that iloprost infusion provided hemodynamic benefit when administered at an adequate dosage that could be tolerated by patients. Given the practitioner-independency and ease of implementation, SpO2 measurement may potentially be used as a surrogate tool for ABI in clinical assessment of CLI patients who receive medical therapy.

The present study reports an about 30% increase in ABI measurement in patients receiving a two-week infusion of iloprost for symptomatic treatment of CLI. This effect size may seem to be larger than expected considering that changes in microvascular perfusion would not have been so reflected as pressure changes within major extremity vessels. However, based on the variability of blood pressure in an individual or even variability of the measurements by observer, usefulness of ABI measurement has been questioned previously; Matzke et al [12] reported an about 15% deviation from the mean. Moreover, there have been only a few studies reporting ABI measurements after iloprost infusion therapy. One study by Ay et al [13] reported a mean of about 16% increase in ABI values after iloprost treatment whereas almost two fold increase was also reported in a recent study by Cevirme et al. [14]. Therefore, our results and those of others above awaits confirmation by further study.

In a previous study, Karabay et al [5] found that ABI values showed a 33% increase in 44 patients with CLI after iloprost administration. Authors reported that anaglesic requirement disappeared in 42/44 patients within 24 hours and in remaining two patients within 48 hours after the treatment began. Guo X et al [15] conducted a prospective study on 298 patients and suggested that despite its reliability still remains in common, ABI showed a decreasing tendency with increasing severity of lesions. Moreover, Stein et al. [16] reported that ABI measurement may neglect the diagnosis of PAOD when measured at rest, as it is commonly recommended. This inconsistency in ABI measurements may be misleading in patients with CLI because, as it is known, clinical severity is not only dependent on the degree of stenosis but also additional features including presence of consecutive lesions and adequacy of collateral circulation. To us, it is reasonable seeking a surrogate tool against ABI in patients with advanced disease as in the case of CLI.

Joyce et al, in an earlier study [17] found a significant correlation between partial oxygen saturations and arteriography views in patients with lower extremity ischemia. In our study, presence and severity of the PAOD was confirmed by angiographic study and our finding that mean SpO2 was quite low in patients with CLI seems compatible with those reported earlier [Table II].

Jawahar et al [18] reported that pulse oximetry had lower sensitivity when compared to ABI when used as a reference test. Moreover, Alvarez et al [19] reported in a population based study that SpO2 was unreliable as a diagnostic screening tool having a low sensitivity [12%] and low specificity [67%] for diagnosis of PAOD. However another study showed that pulse oximetry had 77% sensitivity and 97% specificity for diagnosis of PAOD in diabetic patients and concluded that pulse oximetry had comparable accuracy to ABI [7].

More recently, Kwon et al [6] reported that SpO2 values significantly increased after open or endovascular revascularization and also noted that SpO2 values showed significant correlation with ABI values in all patient groups before the treatment whereas, the correlation after the treatment was only present in patients received endovascular or surgical

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**Table 2: Changes in ABI and SpO2 values after iloprost treatment.**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean ± SD</th>
<th>Mean ± SD/Percentage change</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABI – Before treatment</td>
<td>0.45±0.12</td>
<td>26.19±17.28%</td>
</tr>
<tr>
<td>ABI – After treatment</td>
<td>0.55±0.11</td>
<td>18.5±5.6%</td>
</tr>
<tr>
<td>%SpO2 – Before treatment</td>
<td>78.7±2.96</td>
<td></td>
</tr>
<tr>
<td>%SpO2 – After treatment</td>
<td>93.21±3.25</td>
<td></td>
</tr>
</tbody>
</table>

P<0.001 for ABI difference between before and after treatment; p<0.001 for %SpO2 difference between before and after treatment;

ABI; ankle brachial index, SpO2; peripheral oxygen saturation measured by pulse oximetry.

**Table 3: Correlation among study parameters.**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Improvement in walking</th>
<th>Pain relief</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage change in SpO2</td>
<td>Spearman rho</td>
<td>0.298</td>
</tr>
<tr>
<td>P value</td>
<td>0.053</td>
<td>0.003</td>
</tr>
<tr>
<td>Percentage change in ABI</td>
<td>Spearman rho</td>
<td>0.174</td>
</tr>
<tr>
<td>P value</td>
<td>0.269</td>
<td>0.467</td>
</tr>
</tbody>
</table>

ABI; ankle brachial index, SpO2; peripheral oxygen saturation measured by pulse oximetry
treatment. In this study SpO2 values showed about 16% increase which is similar to the increase we observed. In summary, this study showed that SpO2 is a useful tool assessing revascularization while ours pointed out its benefit in patients receiving medical therapy alone.

STUDY LIMITATIONS

Our study had many limitations including low number of patients, lack of control group, non-randomized design and retrospective data collection. Clinical assessment has not been quantified in numbers which limits drawing definitive conclusions upon study results. Although patient inclusion was based on certain limitations in this study, patients with CLI had many baseline risk factors which may have confounding effects on results or may alter the responsiveness to the therapy.

CONCLUSION

As a conclusion, a two-week treatment of iloprost infusion resulted a significant increase in hemodynamic variables including ABI and SpO2 in patients who were unsuitable candidates for surgical or endovascular revascularization despite the clinical benefit remained limited. Iloprost infusion provided pain relief in only about half of the patients in whom the increase in SpO2 values was more prominent, indicating that pulse oximetry may have a potential for being a surrogate tool for assessment of clinical outcomes in patients receiving medical therapy for CLI.

REFERENCES

7. Parameswaran GI, Brand K, Dolan J. Pulse oximetry as a potential screening tool for lower extremity arterial disease in asymptomatic patients with diabetes mellitus. See comment in PubMed Commons below Arch Intern Med. 2005; 165: 442-446.