Comparison Between Alprostadil and Iloprost in Intravenous Treatment of Patients With Chronic Peripheral Arterial Disease

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ABSTRACT

Introduction: chronic peripheral arterial disease (PAD) seems to be a “rediscovered” pathology nowadays, brought into spotlight by its strong correlation with other significant cardiovascular disorders.

Objectives: to sustain a real benefit from treatment with i.v. prostaglandins (PG) in PAD patients and to directly compare the currently used PG: alprostadil and iloprost.

Method: open, non-randomized cohort study, with placebo group (“classical therapy”) reviewing 615 PAD patients with therapeutic approach during 2003-2012 period, divided in 3 subgroups: “classical” therapy; “classical” therapy + iloprost; “classical” therapy + alprostadil; patients with Burger’s disease were excluded; multiple factor analysis with statistical results inserted.

Results: clear domination of male gender patients, with older female gender patients (p≤0.001); smoking like major risk factor in male and in all patients (p< 0.0001); 124 patients underwent angiography.

Conclusion: a real improvement in the clinical status of patients receiving i.v. prostaglandin therapy with no differences between genders, diabetic and non-diabetic patients; alprostadil seems better than iloprost.

Keywords: Peripheral arterial disease, prostaglandins, iloprost, alprostadil.

BACKGROUND

Chronic peripheral arterial disease (PAD) seems to be a “rediscovered” pathology, being strongly correlated with other significant cardiovascular disorders (1-3).

Despite this, newly guidelines come with no major news: the “classical” therapy takes into account the well-known, but not spectacular in results, naftidrofuryl, pentoxifylline, L-carnitine, while buflomedil drops out in many countries (4,5); a salutary note is the absence of contraindication for beta blockers as associated therapy; statins can increase walking perimeter, but in indirect relationship with PAD stage; antiplateles seems to be more effective in reduction of associated cardiovascular risk than in increase of walking perimeter (6); i.v. prostaglandins had only a simple notice (near inositol and proteoglycans) like other therapies, with-
out conclusive results. An important note is the citation of cilostazol (100 mg twice daily) to improve pain-free walking perimeter in a 2015 update (7).

**OBJECTIVES**

Sustaining a significant role of i.v. PG in the treatment of PAD patients, in a study on a total number of 615 patients diagnosed and treated for PAD (stages II A-IV) in the Department of Internal Medicine – “Sf. Spiridon” Emergency Clinical Hospital Iasi, during 2003-2012 period. It was a cohort prospective non-randomized open study, with placebo group ("classical therapy").

**MATERIAL AND METHOD**

Standard protocol for diagnosis and treatment of PAD patients in our clinic included: clinical evaluation with subsequent angiography in patients with stage III – IV (exception for patients with severe associated comorbidities or those which refused the invasive approach); in stage II B angiography was facultative (we preferred to initiate medical therapy; invasive approach only if after one-month-therapy the evolution was unfavorable). Post-angiography remained two options: by-pass surgery or conservative therapy (+/- sympathectomy) in patients with no surgical solutions or which refuse this solution.

"Classical" therapeutic protocol included a combination between: calcium channel blockers (amlodipine 5-10 mg/day or diltiazem 120-360 mg/day), antiplatelet therapy (ASA 75-150 mg/day and/or clopidogrel 75 mg/day), LMWH (low molecular weight heparin) – fraxiparine/ enoxaparine- in therapeutic doses (in III and IV stages PAD patients), pentoxifylline extended-release 1200 mg/day, statins (simvastatin 40-80 mg/day or atorvastatin 40-80 mg/day or rosvastatin 20-40 mg/day) +/- ACE inhibitors (correlated with the level of systemic blood pressure – ramipril 5-10 mg/day or perindopril 5-10 mg/day or quinapril 5-20 mg/day or zofenopril 15-30 mg/day) (8-11).

Non-surgical solution is dedicated for patients in II A stages, for patients in II B stages with favorable evolution under conservative therapy and for patients in stage III and IV in presence of absolute/ relative contraindication for by-pass (see above).

Due to significant costs, iloprost/ alprostadil therapy was reserved for the following cases:

a. for iloprost – patients in stage II B and III with unfavorable evolution under “classical” therapy; per primam (+/- sympathectomy) in stage IV PAD patients;

b. for alprostadil – patients in stage II B with unfavorable evolution under “classical” therapy; per primam (+/- sympathectomy) in stage III and IV PAD patients.

"Classical" therapy can be initiated and continued in hospital as well as at home. I. v. prostaglandins therapy should be best initiated in hospital, and continued at home after 5-7 days.

Iloprost and alprostadil are synthetic prostaglandins analogues (PGI2/PGE1) with i.v administration and significant action in improvement of endothelial dysfunction at the micro- and macrovascular level. In women, pregnancy must be excluded before start therapy; recommendation for administration must be strictly forward.

**RESULTS**

A. Tabel1. Demographic data

<table>
<thead>
<tr>
<th></th>
<th>Males</th>
<th>Females</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number</td>
<td>569</td>
<td>46</td>
<td>≤ 0.0001</td>
</tr>
<tr>
<td>Median age (years)</td>
<td>63.3 +/-11.4</td>
<td>66.6 +/-11.3</td>
<td>0.0007</td>
</tr>
</tbody>
</table>

B. Tabel 2. Presence of major cardiovascular risk factors:

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Males</th>
<th>Females</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking</td>
<td>538 (94.6%)</td>
<td>29 (62.3%)</td>
<td>≤0.0001</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>273 (48%)</td>
<td>36 (78%)</td>
<td>0.02</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>272 (47.8%)</td>
<td>20 (43.3%)</td>
<td>NS</td>
</tr>
<tr>
<td>Elevated blood pressure</td>
<td>304 (53.5%)</td>
<td>43 (48.7%)</td>
<td>NS</td>
</tr>
<tr>
<td>Age ≥ 55/65 years</td>
<td>351 (61.5%)</td>
<td>27 (57.6%)</td>
<td>NS</td>
</tr>
<tr>
<td>Familial/personal history of cardiovascular disease</td>
<td>380 (66.8%)</td>
<td>42 (91%)</td>
<td>0.03</td>
</tr>
</tbody>
</table>
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C. Table 3. Leriche-Fontaine classification of PAD

<table>
<thead>
<tr>
<th>Stage</th>
<th>Males</th>
<th>Females</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIA</td>
<td>174 (21.1%)</td>
<td>10 (11.3%)</td>
<td>0.065</td>
</tr>
<tr>
<td>IIB</td>
<td>103 (18.1%)</td>
<td>11 (23.9%)</td>
<td>NS</td>
</tr>
<tr>
<td>III</td>
<td>204 (34.2%)</td>
<td>19 (41.3%)</td>
<td>NS</td>
</tr>
<tr>
<td>IV</td>
<td>88 (14.8%)</td>
<td>6 (13.4%)</td>
<td>NS</td>
</tr>
</tbody>
</table>

D. Angiography: 116 males (19.5%) and 8 females (17.4%) underwent angiography.

E. Evolution of conservative treatment possibilities induced the following results:

- 292 patients received "classical" initial therapy:
  - 184 patients (174M/10F) in stage IIA with good evolution (only 6 with deterioration over time);
  - 60 patients (56M/4F) in stage IIB: 39 with improvement in clinical status and regression to IIA stage, 15 with stationary evolution, remaining in IIB stage, 16 with deterioration over time;
  - 34 patients (28M/6F) in stage III: 16 with improvement in clinical status, 18 with deterioration over time;
  - 14 patients (11M/3F) in stage IV: all with severe evolution and need for amputation.

- 60 patients received iloprost therapy:
  - 34 patients (31M/3F) in stage IIB, with spectacular evolution and increase in walking perimeter: 162 meters +/- 56 meters, after 15-20 days of treatment (p=0.008 vs. "classical" therapy);
  - 19 patients (15M/4F) in stage III: all with good evolution and increase in walking distance: 138 meters +/- 42 meters after 15-20 days of treatment (some of them with associated sympathectomy) (p=0.04 vs. "classical" therapy);
  - 7 patients (6M/1F) in stage IV: all with associated sympathectomy; 1 with no amputation need; 6 with low level of amputation compared to "classical" therapy after 15-20 days of treatment (p=0.065 vs. "classical" therapy);

Long term follow-up (28-38 months) shows favorable evolution, with only 2 patients needing amputation. Concerning side effects, the most unpleasant one was headache, induced especially by the maximal doses – 18 patients; most frequent adverse effect (50 from 60 patients) was skin flushing of the cephalic extremity; a rarely adverse effect was significant abdominal discomfort, in one case generating treatment stop; another unpleasant phenomenon – superficial phlebitis at the level of catheterised veins which required frequent changing of peripheral venous catheter position was present in 23 patients; 2 patients presented shivering; dyspnea together with bipsilateral pulmonary rales (non-cardiogenic incipient pulmonary edema) was present in 4 patients. (11). Even if theoretically, through platelets inhibition, concomitant administration with heparin and/or antiaggregants increases the bleeding risk, we did not observed this fact in our patients.

- 263 patients received alprostadil therapy:
  - 20 patients (15M/5F) in stage II B: immediately spectacular results, with medium increase in walking perimeter with 250 meters +/- 40 meters after 20-30 days therapy (p≤0.005 vs. iloprost);
  - 170 patients (161M/9F) in stage III: 142 patients with good clinical evolution and improvement in walking perimeter with 191 meters +/- 33 meters; 7 patients needed amputation (p = ns vs. iloprost); the remaining patients underwent sympathectomy followed by good evolution;
  - 73 patients (70M/3F) in stage IV: 32 with lesions resolution (13 with associated sympathectomy) (p=0.046 vs. iloprost); 31 needed amputation (p=0.055 vs. iloprost); 10 were revascularised with good evolution.

On long term follow-up (14-28 months) only 5 patients had a bad evolution with amputation; the other ones maintained (94 cases) or improved (164 cases) the clinical status achieved after the first approach.

A remarkable phenomenon, more pregnant for alprostadil than for iloprost, is the appearance of what we have named "clear delimitation of viable tissue" observed at PAD patients in stage III and IV. Indeed, after the first days of
treatment it appears a clear delimitation between the viable and non-viable tissue. So, it can be noted that the patient’s response after a few days of therapy (sometimes even after first day), could predict an accurate prognosis.

Concerning the adverse effects, alprostadil is associated with significantly less side effects in comparison to iloprost treated patients: significant headache - only 2 patients (p=0.0002 vs. iloprost); abdominal discomfort with treatment cessation – 1 patient (p=0.001 vs. iloprost); superficial phlebitis at the level of catheterised veins which required frequent changing of peripheral venous catheter position was present in 4 patients (p=0.003 vs. iloprost); 11 patients presented shivering (p=0.03 vs. iloprost); dyspnea together with bisibilar pulmonary rales (non-cardiogenic incipient pulmonary edema) was present in 10 patients (p=0.01 vs. iloprost); skin flushing of cephalic extremity was rarely observed (22 patients - p=0.0001 vs. iloprost); one patient encountered severe hypotension (ns vs. iloprost). Even if theoretically, through platelets inhibition, concomitant administration with heparin and/or antiaggregants increases the bleeding risk, we did not observed this fact in our patients, similar to those treated with iloprost.

**CONCLUSION**

The present study proves additionally benefits by combining “classical” therapy with i.v. prostaglandins, with no significant differences in prostaglandins effects between genders or regarding presence/absence of diabetes mellitus (19).

Regarding the comparison between the two currently used prostaglandins, the superiority of alprostadil versus iloprost is sustained by superior improvement in walking perimeter, quickly installed results, rarely side effects and the so-called “clear delimitation of viable tissue” phenomenon under perfusion with alprostadil in stage III and IV PAD patients.

For patients in stage IV PAD, without surgical solutions, the association between i.v. prostaglandins and sympathectomy seems to offer a maximum benefit.

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**REFERENCES**


