

Effects of micronized purified flavonoid fraction (Daflon) on pelvic pain in women with laparoscopically diagnosed pelvic congestion syndrome: a randomized crossover trial

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Summary

Background: We evaluated the effects of daflon, a venomimetic agent that regulates the circulatory tonus of the venous system, on pelvic pain and investigated the role of enlarged veins in the pathophysiology of pelvic congestion syndrome. **Methods:** Twenty women (age 28-35 yrs) with chronic pelvic pain were diagnosed with the syndrome at laparoscopy. They all had prominent broad ligaments and ovarian veins without other pathologies such as endometriosis to explain the etiology of pelvic pain. Ten women were randomized in a fashion to receive 500 mg of Daflon twice/daily for six months, and ten a vitamin pill for placebo effect; they were crossed over for another six months. **Results:** At the end of the third month, the frequency and severity of pelvic symptoms began to decrease with daflon compared with the pretreatment and vitamin arm. The mean scores were significantly less at the end of six months, respectively, $p < 0.05$. **Conclusions:** Pharmacologic enhancement of venous tonus may restore pelvic circulation and relieve pelvic symptomatology.

Key words: Pelvic congestion; Daflon; Chronic pelvic pain.

Introduction

The syndrome of chronic pelvic pain without an obvious pathology has been described as pelvic congestion syndrome. In the 1940s and 1950s, Duncan and Taylor [1] reported extensively on the findings of venous pelvic congestion in women with pelvic pain. They reported that increased anxiety in women with no pelvic disease resulted in an increase in vaginal blood flow. Typical symptoms of pelvic congestion include lower abdominal and back pain, deep dyspareunia and post-coital pain, abnormal bleeding, chronic fatigue, and exacerbation of pain after prolonged standing. Pain usually begins with ovulation and lasts until the end of menses. Transuterine venography is the standard method for diagnosis [2]. Although the importance in the pathophysiology of pain is uncertain, pelvic ultrasonography with Doppler flow studies or laparoscopy may show prominent enlarged broad ligament veins [3, 4]. Treatment options of presumptive pelvic congestion range from hormonal suppression and cognitive behavioral pain management to hysterectomy.

We evaluated the effect of Daflon (micronized purified flavonoid fraction), a venomimetic agent that regulates the circulatory tonus of the venous system, on pelvic pain and investigated the role of enlarged veins in the pathophysiology of pelvic congestion syndrome.

Materials and Methods

Patients with chronic pelvic pain were evaluated by pelvic examination, high-resolution transvaginal ultrasound examination (TVUS), and laparoscopy. Following pelvic examination,

all patients were examined by TVUS/Doppler to exclude organic pathology such as uterine and adnexal. All patients received various treatment modalities. The patients who still complained of pelvic pain with no improvement in severity or who reported increase in symptoms despite previous treatments were examined by laparoscopy. All patients underwent laparoscopy in the follicular phase, under general anesthesia with the three-puncture technique. During surgery, any possible cause found was treated simultaneously and therefore patients were excluded from the study groups.

Pelvic varicosities were visualized by decreasing the intra-abdominal pressure and gradually replacing the patient in the reverse Trendelenburg position as described by El-Minavi *et al.* [5]. Patients who had a prominent enlarged broad ligament and ovarian veins without any other pathologies such as endometriosis that might explain the etiology of pelvic pain were included in the study. The women in each group received either micronized purified flavonoid fraction (MPFF; Daflon), 500 mg twice/daily for six months ($n: 10$) or a vitamin pill for placebo effect ($n: 10$). Treatments were then crossed over for a further six months. Patients were asked to score the frequency and severity of lower abdominal pain and dyspareunia on a scale from 0 to 6. Pelvic pain scores were evaluated at the end of each menstrual cycle throughout the study and results were compared with pretreatment values with and within the groups.

Statistical analysis was performed using parametric and non-parametric tests where appropriate. A p value < 0.05 was accepted as significant.

Results

Twenty patients were diagnosed as having pelvic congestion syndrome by laparoscopy. The mean age of the patients was 31.4 ± 2.6 years and the demographic variables are depicted in Table 1. Interestingly all patients with pelvic varicosities were multiparous and had suf-

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Table 1. — Demographic characteristics of patients studied during initial randomization to either Daflon (Group A) or vitamins (Group B) (* $p > 0.05$).

	Group A (mean \pm SD)	Group B (mean \pm SD)
Age (yrs)	32.3 \pm 1.7	33.7 \pm 2.1
Body weight (kg)	65.3 \pm 4.7	64.9 \pm 5.1
Gravida	3.4 \pm 1.2	3.1 \pm 1.9
Pelvic scores	5.1 \pm 0.9	4.9 \pm 0.7
Duration of pain (months)	18.1 \pm 4.5	19.3 \pm 6.1
Hx of peripheral varicosities	70%	80%

ferred from pelvic pain more than 12 months despite various medical treatments including oral contraceptives and nonsteroidal anti-inflammatory agents. Compared with the preoperative data, 85.7% (24/28) patients with increased vascularity with Doppler studies were diagnosed with prominent veins during laparoscopy. Four patients who had concomitant endometriosis were excluded from the trial.

Improvements in pelvic scores were evident during the second and third months of Daflon treatment. At the end of the sixth month, there was a significant improvement in pelvic scores of all symptom categories compared with pretreatment scores and the vitamin group scores during treatment with Daflon. Similar results were obtained in the other group when switched to daflon for the second half of the study (Figure 1).

Discussion

Chronic pelvic pain (CPP), common in women in the reproductive age group, causes disability and distress and has vast psychosocial and economic consequences. Usually CPP is associated with varying physiological dysfunctions. It has a prevalence of 15% in reproductive age with a poorly understood pathogenesis [4, 6, 7].

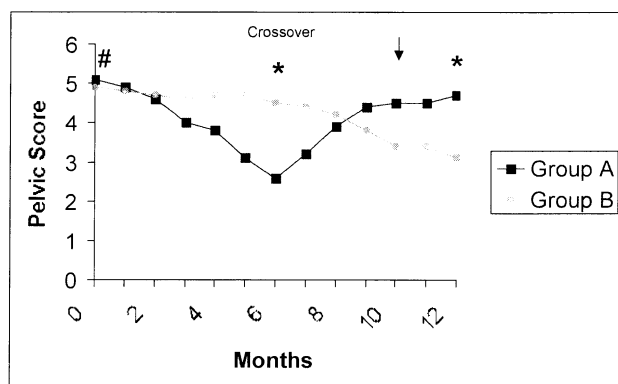
Laparoscopic evaluation is usually considered a routine part of the evaluation in CPP. A patient with CPP may be

a candidate for laparoscopy if conservative forms of therapy (namely anti-inflammatory drugs, antibiotics, psychotherapy, and endocrine suppression) have been unsuccessful. However, objectively the decision for laparoscopy should be based on the patient's history, physical examination, and findings of non-invasive tests including psychological. In the majority of CPP cases, at least a diagnosis that may attribute causality to etiology may be found by laparoscopy [8-10].

Pelvic congestion syndrome (PCS) is an uncommon and frequently overlooked cause of CPP. The well-described clinical presentation is that of pain and fullness exacerbated by prolonged standing, coitus, and in the premenstrual period in multiparous women. Pelvic examination reveals tenderness without induration or masses [3, 10, 11]. Furthermore Fry *et al.* [12] reported significant associations emerging among some social arrangements, paternal parenting, and patterns of hostility in the group with pelvic venous congestion. Transuterine venography is the standard method for diagnosis [2, 3, 11]. Although their importance in the pathophysiology of pain is uncertain, pelvic ultrasonography with Doppler flow studies or laparoscopy may show prominent enlarged broad ligament veins.

Pelvic congestion could be more than an expected finding that should not be overlooked in women with CPP especially in multigravidas. Detailed history and pelvic examination along with psychological interventions are complementary to the diagnosis and may lead physicians to further diagnostic tools such as venography in CPP with negative laparoscopy findings. The subgroup of CPP cases who underwent laparoscopy in the present study were diagnosed as having PCS by using the strict criteria of a prominent broad ligament and/or ovarian veins without any other pathology. Moreover, preoperative TVUS and Doppler findings have supported the role of laparoscopy. Since there are reports of PCS with negative laparoscopy findings, the cases with symptoms presumptive of PCS who had negative laparoscopy should be further tested to outline underlying pelvic venous incompetency [13]. Our results are further supportive of the above suggestion since only 85% of cases who had positive Doppler findings preoperatively were diagnosed with pelvic varicosities during laparoscopy in the present trial. Thus, diagnosis of pelvic venous dysfunction without gross dilated veins can be guided with more sensitive approaches such as venography and magnetic resonance imaging in typical symptomatic patients with no prominent findings at laparoscopy. However as reported by El-Minawi *et al.* [5] physicians should be aware that posture and intraabdominal pressure may obscure the visualization of pelvic varicosities.

The role of venomimetic agents in PCS with pelvic venous insufficiency was reported to have a major role in pathogenesis. Since peripheral venous insufficiency is also reported in PCS cases, Daflon (MPFF), a well-established oral flavonoid that consists of 90% micronized diosmin and 10% flavonoids expressed as hesperidin, a potent venotropic drug used in the treatment of venous



Group A: Started with Daflon and then did crossover to vitamins for placebo effect

Group B: second arm of the study group received vitamins for six months and switched over to Daflon in the second half of the study.

insufficiency, was used in this trial. Pharmacological and clinical studies demonstrated the comprehensive mode of action of 500 mg of Daflon: it increases venous tone, improves lymph drainage, and protects the microcirculation by inhibiting the synthesis of prostaglandins (PG) and free radicals and by decreasing bradykinin-induced microvascular leakage [14-16]. Moreover, PG inhibiting effects may further alleviate the pain by reducing uterine contractility. Our trial demonstrated significant improvement in pelvic pain scores with Daflon treatment compared to the placebo effect of vitamins. Particularly, coital problems were alleviated with the treatment in all but two cases who had vast family problems.

Based on our preliminary results, we conclude that venous dysfunction and stasis may be pathophysiologic components of pelvic pain in women with pelvic congestion syndrome. Furthermore, the role of laparoscopy in CPP is supported with the present trial. However, in CPP cases where no pathology was found during laparoscopy, a detailed history and nature of symptoms along with normal pelvic examination supports the possibility of PCS and requires further diagnostic tests such as venography, etc. In cases with PCS initial pharmacologic enhancement of venous tonus may restore pelvic circulation and relieve pelvic symptomatology.

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