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Research Article

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Dopaminergic Drug Very Effective for Relieving Pelvic Pain in Women Even When Hormonal Therapy and Surgery Were not Sufficient

Jerome H. Check[1,2*], Paul Carpentier[3], Barbara Meier[3] and Naomi Ganpo-Nkewnkwa[1]

[1]*Cooper Medical School of Rowan University, Dept. OB/GYN. Div. Repro, Endo. & Infertility, Camden, NJ, USA*

[2]*Cooper Institute for Reproductive Hormonal Disorders, P.C. Mt. Laurel, NJ, USA*

[3]*The Long Island Gianna Center for Women's Health and Fertility, Babylon, NY, USA*

[*]**Corresponding author**

Jerome H Check, MD, Ph.D. Cooper Medical School of Rowan University, Camden, NJ, USA. TEL: 215-635-4400, FAX: 215-635-2304

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ABSTRACT

There have been multiple case reports demonstrating marked relief of various pelvic disorders following treatment with dopaminergic drugs especially dextroamphetamine sulfate. The theoretical reason for treating pelvic pain, including women with documented endometriosis and adenomyosis, was based on experimental evidence that dopamine functions to diminish cellular permeability; and that increased cellular permeability of pelvic tissues, whether genetic or acquired from infection or trauma, allows the infusion of excessive irritants leading to inflammation and pain. Most of these anecdotal reports have come from mainly one reproductive endocrinology clinic. The present study reported here was to either corroborate or refute the concept that dopaminergic drugs are very effective to relieve pain even when standard therapy has failed, by a completely different gynecology center. More than half of the patients had prior laparoscopic treatment of endometriosis, and all had various standard medical therapies that failed. 17 of 25 (68.0%) reported marked relief of pain and 2 others reported moderate relief (76% marked or moderate relief after 3 months of therapy). Experience suggests that most of the remaining 25% would gain relief by increasing the dosage. The advantage of dopaminergic therapy besides being more effective for pain relief than standard medical therapy or surgery is that not only can the patient try to conceive while on it, but evidence suggests it will improve fertility by inhibiting immune rejection. Dopamine antagonists may also prevent a decrease in egg reserve by interfering with inflammatory damage.

Keywords: Adenomyosis, Vulvovaginitis, Interstitial Cystitis, Dopaminergic Drugs, Dysmenorrhea

Introduction

Post-ovulation, it is important to allow normal embryo implantation by helping the conversion of some thick-walled uterine arteries into thin-walled spiral arteries to allow nutrient exchange between mother and fetus [1]. There is evidence that this inflammatory response is initiated by the progesterone secreted by the corpus luteum which inhibits dopamine, thus allowing irritants to infuse into the uterus which in turn stimulates an inflammatory response [1,2]. Dopamine functions to suppress cellular permeability [1-3].

Exaggeration of an increase in cellular permeability may lead to excessive infiltration of irritating elements, leading to excessive inflammation, with subsequent pelvic pain associated with conditions including endometriosis and adenomyosis. Thus, medication that releases more dopamine from sympathetic nerve fibers may diminish excessive cellular permeability with consequential decreased inflammation and diminished pain not only in the pelvis, but in other areas of the body [4,5].

Dextroamphetamine sulfate is a medication that releases more dopamine from sympathetic nerve fibers. There have been several anecdotal case reports claiming that dopaminergic drugs can ameliorate many different types of pelvic pain including chronic pain and sciatica, and pelvic pain of bladder origin [6-18].

All these aforementioned studies seem to come from one reproductive endocrinology center. A search of the literature failed to find other studies from different treatment centers, either corroborating, or refuting the statement that dextroamphetamine sulfate therapy can significantly reduce pelvic pain. Thus, this prospective study was performed in a different treatment center to determine if this beneficial effect could be corroborated or not.

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Materials and Methods

Patients complaining of significant pelvic pain were recruited. All had moderate to severe pain. It was ascertained if they had failed previous medical therapy, including non-steroidal anti-inflammatory drugs, progestin therapy (oral contraceptives, norethindrone, etc.), estrogen suppression with gonadotropin releasing hormone agonists (e.g., leuprolide acetate), they were prescribed 20-30mg extended-release dexamphetamine salts capsules every morning providing 12.5-37.6mg of dextroamphetamine sulfate. They were re-evaluated in 3 months and questioned as to whether they had 1) marked relief or pain, 2) moderate relief of pain, or 3) little or no relief.

Results

Thirty-one women were recruited for the study. All 31 had previously used NSAIDS, and 27 of 31 had previously unsuccessfully been treated with oral contraceptive, progestins, progesterone, or leuprolide acetate. Six dropped out for various reasons. 17 of 25 (68%) reported that the pain markedly improved; an additional 2 found moderate relief. After 3 months, a total of 76% of patients on a relatively small dosage of dextroamphetamine sulfate had moderate to marked relief of pain.

Discussion

Our position on treating pelvic pain and endometriosis with the goal of correcting infertility and/or preventing miscarriage is that the first choice of treatment should be dopaminergic drugs [4]. Our group published one of the earliest studies providing evidence that laparoscopic removal of even mild endometriosis could improve fecundity [19]. Not all studies agree, but we still think that somehow the presence of actual endometrial implants does exacerbate the increased cellular permeability leading to more infiltration of unwanted irritants causing more pain. Thus, if one quickly corrects other infertility factors (e.g., luteal phase defects), it can increase the pregnancy rates in the first 3-4 months after surgery before the degrees of infiltration of irritants return.

The question arises in women who have pelvic pain trying to get pregnant or who eventually want to conceive, whether the type of pain is dysmenorrhea, pre-menstrual pelvic pain, chronic pelvic pain, interstitial cystitis, dyspareunia or mittelschmerz, or pre-menstrual dyschezia should a laparoscopy be performed to at least establish a diagnosis? Our view is that, in general, a laparoscopic diagnosis is not necessary and can be detrimental to the health of the patient. Chronic inflammation causing pelvic pain with or without the ectopic implantation of endometriotic lesions (probably related to the permeability defect in the endometrium) is the most common cause of diminished ovarian reserve (DOR) or premature ovarian failure (POF) [20]. We would treat a woman who is not finished with procreation with dopaminergic drugs not to just relieve pain but to enhance fecundity and help retard the acceleration of egg loss. Thus, diagnosing endometriosis by laparoscopy is not necessary because its presence or not would not influence management options.

One could argue that if one sees endometriosis the removal of it could relieve the pain sufficiently so that treating with dopaminergic drugs may not be necessary. However, laparoscopic removal of endometriosis may directly damage ovarian tissue if lesions are present on the ovary or damage blood supply to the ovaries, further accelerating DOR. Thus, our policy at Cooper Institute for Hormonal Disorders is to consider a laparoscopy for women with pelvic pain who have failed to conceive with methods seemingly correcting well-known infertility factors, where there is consideration that despite the demonstration of tubal patency by hysterosalpingography, the possibility of tubal adhesions does exist. For some couples whose insurance pays for invitro-fertilization-embryo transfer (IVF-ET) or where couples can afford the procedure, they may choose IVF-ET at this time. However, for some couples their insurance will pay for laparoscopic surgery but not IVF, so this is when we typically will do a laparoscopy with the aim of surgically removing scar tissue and endometriosis at that time.

Many of the women in the study presented may have already had all the children that they wanted and just wanted to be treated for their pelvic pain. To present a second opinion concerning treatment options, we chose a review by Patricia Ribeiro de Carvalho Franca et al entitled, “Endometriosis: a disease with few direct treatment options” [21]. They state that the choice of treatment will depend on the severity of symptoms, the extent and location of the disease, the desire to become pregnant, and the patient’s age. They mention that the treatment can be through medication, surgery, or a combination of both [21].

As far as medical therapy, Ribeiro de Carvalho Franca et al., mention oral contraceptives as the first choice which can be given to allow menses or take them continuously to prevent menses in case of severe dysmenorrhea [21]. We would agree at least for the woman no longer interested in procreation, this would be the best option based on lack of expense and, lack of visits to the treating physician (if it is as effective). If, however, there are other extra pelvic manifestations of the increased cellular permeability syndrome, we would still start with a dopaminergic drug, and then only if not completely effective in eradicating pelvic pain, then add an oral contraceptive with or without the presence of estrogen.

Franca et al state that the second line therapy is to make the patient hypoestrogenic by using a gonadotropin releasing hormone agonist (GnRHa) [21]. Examples would include drugs, e.g., depo-leuprolide acetate. Disadvantages of the drugs are 1) great expense 2) not available orally because it is damaged in the digestive system so it must be given parentally by intramuscular or subcutaneous injections or by nasal spray or even intravaginally. Besides expense these drugs induce a pseudo menopause leading to osteopenia/osteoporosis, menopausal symptoms e.g., vasomotor symptoms and eventually thinning of vaginal walls leading to dyspareunia. Thus, if progestin therapy was the first choice, we believe that dopaminergic drugs should be the second option before GnRHa treatment.

The aforementioned review (Ribeiro de Carvalho Franca et al) mentions hyperandrogenism therapy e.g., danazol or gestinone. However, the androgenic side effects, e.g., acne, hirsutism, alopecia, weight gain, and risks of coronary heart disease because of adverse lipid profile, make this therapy much less desirable and mentioned mostly for historical purposes.

This review mentioned the use of aromatase inhibitors usually in combination with progesterone or oral contraception. It can be taken orally e.g. anastrozole or letrozole. About 50% of patients taking aromatase inhibitors develop bone pain. Aromatase inhibitors and oral contraception are a reasonable treatment option as long as the symptoms of the increased cellular permeability syndrome are mostly restricted to the pelvis and because of side effects dopaminergic drugs cannot be used.

Finally, one of the newest treatment options in an orally administered GnRH antagonist, thus causing estrogen deficiency state called elagolix [21]. Not only is the drug expensive, but it can lead to many of the aforementioned side effects of estrogen deficiency such that by 6 months, 70% reported at least one adverse effect during treatment [21].

The aforementioned non-surgical options are the most commonly used treatment options with the exclusion of dopaminergic drugs because of lack of publicity. It is suspected that since there are no profitable options for pharmaceutical companies, it is the least known type of treatment to most clinicians. Nevertheless, in our opinion it is the best treatment option overall for the following reasons: 1) it is the only option that can be used to allow the patient to conceive 2) delaying procreation by shutting off estrogen production results in a group already prone to egg depletion to advance more related to time before attempting to conceive and adds the "adverse consequences" of increased age in those of a significant advanced age already 3) dopaminergic drugs may help to retard egg depletion better than any of the other aforementioned

treatment 4) since pelvic pain frequently co-exists with other co-morbidities that will also respond to dopaminergic drugs this is a distinct advantage since creating an estrogen deficiency state has no beneficial action on other co-morbidities 5) dopaminergic drugs are the least expensive treatment options other than oral contraceptives 6) dopaminergic drugs have the least short term and long term side effects with the exception of oral contraceptives and progestins.

The only situation where we think that oral contraception/ progesterone should be considered first line treatment is the woman with pelvic pain no longer interested in conceiving whose only complaint is pelvic pain. If the oral contraceptive is beneficial, but still not totally effective, then a dopaminergic drug could be added..

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