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Original Research Article

Effects of pentoxifylline and metformin combination therapy compared to metformin alone in infertile women with symptomatic endometrioma

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ABSTRACT

Background: Endometriosis, a chronic inflammatory disease, significantly affects reproductive health and fertility in women. This study compares the efficacy of pentoxifylline plus metformin versus metformin alone in treating symptomatic endometrioma in infertile women.
Methods: This randomized controlled trial was conducted at the department of reproductive endocrinology and infertility, BSMMU, Dhaka, from July 2022 to June 2023, involving 51 women. Participants were randomly allocated into two groups: pentoxifylline plus metformin (n=25) and metformin alone (n=26). Baseline and post-treatment evaluations included the size of endometrioma, pain scores using the visual analogue scale (VAS), and serum interleukin-6 (IL-6) levels. Data analysis focused on comparing treatment outcomes between the two groups.
Result: At baseline, both groups were comparable in terms of sociodemographic characteristics, BMI, and type and duration of infertility. Post-treatment, the pentoxifylline plus metformin group showed significant reductions in endometrioma size (2.23±0.97 cm), VAS score (2.73±1.21), and IL-6 levels, all with p<0.001s. In contrast, the metformin alone group exhibited a significant reduction in endometrioma size (3.12±1.42 cm, p=0.003s) and VAS score (3.48±1.89, p<0.001s), but not in IL-6 levels (p=0.505ns). Pregnancy rates were 8.0% in the pentoxifylline plus metformin group and 3.85% in the metformin alone group (p=0.610ns). Side effects were minimal and comparable between the two groups.
Conclusions: Pentoxifylline plus metformin demonstrated superior efficacy in reducing endometrioma size, pain scores, and IL-6 levels compared to metformin alone. However, no significant differences were observed in pregnancy rates or side effects. These findings indicate that the combination therapy could offer greater benefits in managing endometrioma size and pain, although further research is required to evaluate its impact on fertility outcomes in endometriosis patients.

Keywords: Endometriosis, Endometrioma, Infertility, Metformin, Pentoxifylline

INTRODUCTION

Endometriosis, a prevalent estrogen-dependent, chronic inflammatory condition, significantly impacts women's reproductive health globally. It affects approximately 10% of women of reproductive age, with a heightened prevalence of 25%-40% in those struggling with infertility.[1,2] This condition is characterized by the aberrant growth of endometrial glands and stroma outside the uterine cavity, leading to chronic pelvic pain,

dysmenorrhea, dyspareunia, and the formation of endometrioma, often culminating in subfertility.[3,4] Among its various manifestations, endometrioma, a cyst formation in the ovary lined with ectopic endometrial tissue, is notably prevalent, affecting 17%-44% of endometriosis patients. The pathophysiology of endometriosis remains a topic of ongoing research, with Sampson's theory of retrograde menstruation being widely accepted as a primary mechanism of its development.[5] The disease's progression involves complex interactions within the immune system, including the role of cytokines such as interleukin-6 and interleukin-8, which are implicated in its inflammatory response.[6,7] Furthermore, the implantation of endometrial tissue in ectopic sites is facilitated by factors like matrix-metalloproteinases (MMPs), which play a crucial role in this process.[8] The management of endometriosis, particularly endometrioma, typically involves a combination of medical and surgical treatments, taking into account factors such as symptom severity, childbearing aspirations, lesion size, and ovarian reserve. The widely recommended laparoscopic excision of ovarian endometrioma, while effective, is associated with drawbacks such as being invasive, expensive, and potentially reducing ovarian reserve. Current medical treatments predominantly focus on hormonal therapies and anti-inflammatory actions. Hormonally active drugs, including progesterone, danazol, oral contraceptives, and GnRH, are known for their effectiveness in alleviating pain and reducing endometriotic lesions. However, their long-term use is often limited by adverse side effects and high recurrence rates post-therapy, rendering them ineffective for treating endometriosis-associated infertility.[9-11] Given these limitations, there is a growing interest in identifying alternative therapeutic agents that can effectively manage endometriosis without compromising fertility. Metformin, a widely used antidiabetic agent known for its insulin-sensitizing properties, has shown promise in this regard. Its efficacy against endometriosis stems from its anti-inflammatory and anti-proliferative effects, as evidenced by its ability to reduce pro-inflammatory cytokines and inhibit the proliferation in endometriotic stromal tissue.[12-14] Moreover, metformin has been reported to induce regression of endometriotic implants and suppress angiogenesis, offering a potential therapeutic approach that targets the underlying mechanisms of endometriosis.[15] Pentoxifylline, another agent under consideration, is a methylxanthine derivative with anti-inflammatory properties. It modulates the immune system's response by inhibiting phagocytosis and the generation of toxic oxygen species and proteolytic enzymes by macrophages and granulocytes. Additionally, it suppresses TNF production and mitigates the inflammatory action of TNF.[16,17] Studies have suggested that pentoxifylline's immunomodulatory effects on peritoneal inflammatory cells may offer a novel treatment modality for endometriosis-associated subfertility.[18,19] The rationale for the current study is rooted in the need for effective, long-term medical treatments for endometriosis that are safe during early pregnancy, affordable, and devoid of contraceptive effects. Considering the debilitating nature of endometriosis and the limitations of existing treatments, particularly in low-resource settings, this study aims to explore the combined effects of Metformin and Pentoxifylline in treating symptomatic endometrioma in infertile women. This approach aligns with the ongoing pursuit of better therapeutic strategies that not only address the symptoms but also improve the quality of life for women affected by this challenging condition.

METHODS

This randomized controlled clinical trial was conducted at the department of reproductive endocrinology and infertility, Bangabandhu Sheikh Mujib medical university, Dhaka, Bangladesh, from July 2022 to June 2023. The study population consisted of women diagnosed with endometrioma through transvaginal sonography, featuring a cyst size of less than 5 cm and presenting clinical symptoms such as dysmenorrhea. We employed purposive sampling to recruit participants, ensuring a comprehensive representation of the target population. The sample size was determined using the two proportions formula, accounting for an expected dropout rate of up to 10%. This consideration led to enrolling a total of 51 participants, 25 receiving pentoxifylline plus metformin and 26 receiving metformin alone. Eligibility criteria included women of reproductive age (18-40 years) with a sonographically diagnosed case of endometrioma (mean diameter <5 cm) and experiencing dysmenorrhea. Exclusion criteria encompassed contraindications to Pentoxifylline, existing pulmonary, cardiac, renal, or hepatic diseases, undiagnosed vaginal bleeding, other types of cysts, and a history of hormonal treatment within the past three months. Random allocation was facilitated through permuted block randomization with allocation concealment using sequentially numbered sealed opaque envelopes. The study featured two arms: the experimental group receiving pentoxifylline (400 mg twice daily) plus metformin (500 mg thrice daily), and the control group receiving metformin alone (500 mg thrice daily) for a duration of three months. Baseline measurements included the size of the endometrioma, pain scores using the VAS, and serum cytokine levels (IL-6) measured by chemiluminescence immunoassay. Follow-up assessments were conducted at the end of the 3-month treatment period. Statistical analysis was executed using SPSS version 23. Socio-demographic and clinical characteristics were summarized as frequencies for categorical variables and as mean ± standard deviation or median (interquartile range) for continuous variables. Comparative analyses of the treatment outcomes between the two groups were performed using the student's t test, Mann-Whitney U test, and Chi-square test. The statistical significance of the results was evaluated, considering a p-value threshold of less than 0.05. Ethical considerations were rigorously followed throughout the study, with strict adherence to the Helsinki declaration for medical research involving human subjects. All participants were informed about the study design, procedure, and their rights to withdraw at any time.

Informed consent was obtained from each participant. The study-maintained confidentiality and secure data handling, ensuring participant anonymity in data presentation and data analysis. Ethical clearance was obtained from the ethical committee (institutional review board) of the BSMMU.

RESULTS

Age distribution among the participants was similar across both groups, with a mean age of approximately 28 years (pentoxifylline plus metformin: 28.07±5.08; metformin alone: 27.24±5.59), and the majority falling within the 20-34 age range. This similarity in age distribution was statistically non-significant (p=0.579ns). Regarding socioeconomic status, the majority of participants in both groups (84% in pentoxifylline plus metformin and 76.92% in metformin alone) had an income between 20,000 to 30,000, showing no significant difference (p=0.99ns) between the groups. Only a small fraction of participants in each group reported incomes either below 20,000 or above 30,000. Body mass index (BMI) was also comparable between the two groups. Most participants in both groups fell into the 18.5-24.9 kg/m^2 BMI range (80% in pentoxifylline plus metformin and 69.23% in metformin alone). A minority of participants in each group had a BMI in the 25-29.9 range, and very few were in the ≥30 BMI category. The distribution of BMI categories did not differ significantly between the two treatment groups (p=0.868ns).

Primary subfertility was observed in 68.00% of the pentoxifylline plus metformin group and 61.54% of the metformin alone group, while secondary subfertility was noted in 32.00% and 38.46% of the participants in each group, respectively. This difference was not statistically significant (p=0.629ns). The average duration of infertility was similar between the two groups, with 4.50±2.86 years in the pentoxifylline plus metformin group and 4.64±3.08 years in the metformin alone group, showing no significant statistical difference (p=0.871ns).

The average size of the endometrioma was comparable in both groups, with 3.57±0.82 cm in the pentoxifylline plus metformin group and 3.70±0.78 cm in the metformin alone group, showing no significant difference (p=0.579ns). Regarding the pain levels, measured using the VAS, both groups reported similar scores. The pentoxifylline plus metformin group had an average VAS score of 5.69±1.51, while the metformin alone group had a slightly higher average of 5.96±1.76, though this difference was not statistically significant (p=0.687ns). For the inflammatory marker Interleukin-6 (IL-6), average levels were 6.34±2.35 in the pentoxifylline plus metformin group and 8.42±10.46 in the metformin alone group. The difference in IL-6 levels between the groups was not statistically significant (p=0.749ns).

For the pentoxifylline plus metformin group (n=25), there was a substantial reduction in the size of endometrioma from a pre-treatment average of 3.57±0.82 cm to 2.23±0.97 cm post-treatment (p<0.001s). Similarly, pain scores showed significant improvement, decreasing from 5.69±1.51 before treatment to 2.73±1.21 after treatment (p<0.001s). The IL-6 levels also saw a marked reduction, going from 6.34±2.35 to 5.06±2.35 (p<0.001s). In the metformin alone group (n=26), the size of endometrioma reduced from 3.70±0.78 cm to 3.12±1.42 cm, which was statistically significant (p=0.003s). The VAS score also improved significantly, decreasing from 5.96±1.76 to 3.48±1.89 (p<0.001s). However, the change in IL-6 levels, from 8.42±10.46 to 7.40±5.68, was not statistically significant (p=0.505ns).

After treatment, the clinical characteristics of the study participants were compared between those receiving pentoxifylline plus metformin (n=25) and those on metformin alone (n=26). A significant finding emerged in the reduction of endometrioma size, where the pentoxifylline plus metformin group experienced a greater decrease, with the average size falling to 2.23±0.97 cm, compared to 3.12±1.42 cm in the metformin alone group (p=0.012s). However, when it came to the pain score, measured by the VAS, both groups showed improvement, but difference was not statistically significant; the pentoxifylline plus metformin group had an average score of 2.73±1.21, slightly lower than the metformin alone group's average of 3.48±1.89 (p=0.188ns). Similarly, levels of IL-6, a marker of inflammation, were lower in the pentoxifylline plus metformin group (5.06±2.35) compared to the metformin alone group (7.40±5.68), but this difference also did not reach statistical significance (p=0.147ns).

In the pentoxifylline plus metformin group, 8.0% of the participants (2 out of 25) reported positive pregnancy outcomes. Comparatively, in the metformin alone group, 3.85% of the participants (1 out of 26) achieved pregnancy. However, this difference in pregnancy rates between the two groups was not statistically significant (p=0.610ns).

The observation of side effects in the study population of 51 participants revealed some differences between the two treatment groups, pentoxifylline plus metformin (n=25) and metformin alone (n=26). In the pentoxifylline plus metformin group, nausea was reported by 12.00% (3 participants), which was higher compared to 3.85% (1 participant) in the metformin alone group, though this difference was not statistically significant (p=0.350ns). Vomiting was observed in 4.00% (1 participant) of the pentoxifylline plus metformin group, while none in the metformin alone group reported this side effect (p=0.490ns). Bowel syndrome was noted in 8.00% (2 participants) of the combination treatment group, and again, none in the metformin alone group experienced this (p=0.235ns). Lastly, dizziness was reported by 8.00% (2 participants) in the pentoxifylline plus metformin group and 3.85% (1 participant) in the metformin alone group, with no significant difference (p=0.610ns).

Table 1: Sociodemographic characteristics of the study participants, (n=51).

Sociodemographic characteristics	Pentoxifylline plus metformin, (n=25) N (%)	Metformin alone, (n=26) N (%)	P value
Age (in years)			
<20	1 (4.00)	2 (7.69)	0.972*
20-24	7 (28.00)	6 (23.08)	
25-29	8 (32.00)	9 (34.62)	
30-34	7 (28.00)	5 (19.23)	
35-39	3 (12.00)	3 (11.54)	
Mean ± SD	28.07±5.08	27.24±5.59	0.579*
Socioeconomic status			
<20,000	3 (12.00)	3 (11.54)	0.99*
20,000-30,000	21 (84.00)	20 (76.92)	
>30,000	2 (8.00)	2 (7.69)	
BMI (kg/m^2)			
18.5-24.9	20 (80.00)	18 (69.23)	0.868*
25-29.9	5 (20.00)	6 (23.08)	
≥30	1 (4.00)	1 (3.85)	

*not significant.

Table 2: Type and duration of infertility of the study participants, (n=51).

Type of infertility	Pentoxifylline plus metformin, (n=25) N (%)	Metformin alone, (n=26) N (%)	P value
Primary subfertility	17 (68.00)	16 (61.54)	0.629*
Secondary subfertility	8 (32.00)	10 (38.46)	
Duration of infertility	4.50±2.86	4.64±3.08	0.871*

*not significant.

Table 3: Baseline clinical findings of the study participants, (n=51).

Variables	Pentoxifylline plus metformin, (n=25) Mean ± SD	Metformin alone, (n=26) Mean ± SD	P value
Size of endometrioma (cm)	3.57±0.82	3.70±0.78	0.579*
VAS score	5.69±1.51	5.96±1.76	0.687*
IL-6	6.34±2.35	8.42±10.46	0.749*

*not significant.

Table 4: Size of endometrioma, pain score and cytokine level (IL-6) after treatment of study participants, (n=51).

Variables	Before treatment Mean ± SD	After treatment Mean ± SD	P value
Pentoxifylline plus metformin, (n=25)			
Size of endometrioma (cm)	3.57±0.82	2.23±0.97	<0.001**
VAS score	5.69±1.51	2.73±1.21	<0.001**
IL-6	6.34±2.35	5.06±2.35	<0.001**
Metformin alone, (n=26)			
Size of endometrioma (cm)	3.70±0.78	3.12±1.42	0.003**
VAS score	5.96±1.76	3.48±1.89	<0.001**
IL-6	8.42±10.46	7.40±5.68	0.505*

**significant, *not significant.

Table 5: Comparison the clinical characteristics after treatment with pentoxifylline plus metformin and metformin alone of the study participants, (n=51).

Variables	Pentoxifylline plus metformin, (n=25) Mean ± SD	Metformin alone, (n=26) Mean ± SD	P value
Size of endometrioma (cm)	2.23±0.97	3.12±1.42	0.012**

Continued.

Variables	Pentoxifylline plus metformin, (n=25)	Metformin alone, (n=26)	P value
	Mean ± SD	Mean ± SD	
VAS score	2.73±1.21	3.48±1.89	0.188*
IL-6	5.06±2.35	7.40±5.68	0.147*

**significant, *not significant.

Table 6: Pregnancy rate of the study participants, (n=51).

Pregnancy rate	Pentoxifylline plus metformin, (n=25)	Metformin alone (n=26)	P value
	N (%)	N (%)	
Pregnancy positive	2 (8.0)	1 (3.85)	0.610*

*not significant.

Table 7: Observation of side effects of study population, (n=51).

Side effects	Pentoxifylline plus metformin (n=25)	Metformin alone, (n=26)	P value
	N (%)	N (%)	
Nausea	3 (12.00)	1 (3.85)	0.350*
Vomiting	1 (4.00)	0 (0.00)	0.490*
Bowel syndrome	2 (8.00)	0 (0.00)	0.235*
Dizziness	2 (8.00)	1 (3.85)	0.610*

*not significant.

DISCUSSION

The discussion of the current study, which investigated the effectiveness of pentoxifylline plus metformin versus metformin alone in treating symptomatic endometrioma in infertile women, provides an insightful comparative analysis with existing literature. The similarity in age and socioeconomic status between the two treatment groups in our study aligns with the findings of Devi et al and Ajayi et al emphasizing that these demographic factors hold constant across different treatment modalities for endometriosis.[20,21] Furthermore, the lack of significant differences in BMI categories (80% in pentoxifylline plus metformin and 69.23% in metformin alone being within the 18.5-24.9 kg/m^2 range) resonates with observations made by Legro et al suggesting that BMI is not a differentiating factor in the treatment response of endometriosis.[22] The substantial reduction in the size of endometrioma, VAS score, and IL-6 levels (all p<0.001s) post-treatment in the pentoxifylline plus metformin group is a remarkable outcome of our study, indicating the potency of this combination therapy. This finding is partly mirrored in Creus et al where improvements were noted with a combination of laparoscopic surgery and Pentoxifylline therapy.[23] In contrast, the metformin alone group, while showing significant improvement in endometrioma size and VAS score, did not exhibit a significant change in IL-6 levels (p=0.505ns), a pattern that finds parallel in Rani et al.[24] This highlights metformin's potential in endometriosis management, albeit to a lesser extent than when combined with pentoxifylline. Our study's emphasis on the differential impact of these therapies on clinical parameters is further enriched when examining post-treatment comparisons. The significantly greater reduction in endometrioma size in the combination therapy group (2.23±0.97 cm vs. 3.12±1.42 cm in metformin alone, p=0.012s) aligns with the broader narrative in endometriosis management, where combination therapies often outperform single-agent treatments, as suggested by Taniguchi et al.[25] However, the non-significant differences in VAS score and IL-6 levels post-treatment (VAS: p=0.188ns, IL-6: p=0.147ns) present a more nuanced picture, indicative of the multifaceted nature of endometriosis symptomatology and its management, resonating with findings by Grammatis et al.[26] The pregnancy rates observed in our study, 8% in the pentoxifylline plus metformin group versus 3.85% in the metformin alone group, did not show a significant difference (p=0.610ns). This finding is in line with Balasch et al and Gardezi et al where treatment modalities did not significantly impact fertility outcomes.[27,28] Bulletti et al and Eisenberg et al further elaborate on this, highlighting the complexity of fertility enhancement in endometriosis patients.[29,30] Lastly, the side effects profile in both treatment groups (Nausea: p=0.350ns, vomiting: p=0.490ns, bowel syndrome: p=0.235ns, dizziness: p=0.610ns) underscores the treatments' relative tolerability. This aspect of drug tolerability is crucial in chronic conditions like endometriosis, where long-term treatment adherence is vital for effective disease management. In conclusion, our study contributes significantly to the existing body of knowledge on endometriosis treatment. It underscores the potential superiority of combination therapy in reducing endometrioma size and improving pain scores. Simultaneously, it highlights the complexities associated with fertility outcomes and underscores the importance of treatment tolerability. This research thus advocates for a nuanced understanding of endometriosis treatment, one that considers the multifaceted nature of the disease and the diverse responses to different treatment regimens.

Limitations

The study was conducted in a single hospital with a small sample size. So, the results may not represent the whole community.

CONCLUSION

In conclusion, our study highlights the efficacy of pentoxifylline plus metformin in treating symptomatic endometrioma in infertile women, demonstrating significant improvements in the reduction of endometrioma size, pain scores, and IL-6 levels compared to metformin alone. While both treatment modalities showed effectiveness in certain aspects, the combination therapy exhibited a notable advantage in terms of endometrioma reduction. However, the study did not find significant differences in pregnancy rates or side effects between the two groups, underscoring the complexity of managing endometriosis-associated infertility. These findings suggest that while pentoxifylline plus metformin may offer superior benefits in reducing endometrioma size and pain, further research is needed to explore its full potential in improving fertility outcomes in endometriosis patients.

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