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ORIGINAL RESEARCH

Efficacy of dienogestversus GnRH analogues in the treatment of endometriosis associated pelvic pain: A systematic review and meta-analysis

[1]Dr. Divyapriya Rajendran, [2]Dr. Priyadharshini Durairaju, [3]Dr. Reenaa Mohan, [4]Dr. Jenifer Florence Mary J, [5]Dr. Sruthy P Sulaiman, [6]Dr. Preetha Tamilarasan, [7]Dr. Suja Xaviar

[1]Assistant Professor, Department of Obstetrics and Gynaecology, Sri Manakula Vinayagar Medical College and Hospital, Pondicherry,India
[2]Associate Professor, Department of Obstetrics and Gynaecology, Sri Manakula Vinayagar Medical College and Hospital, Pondicherry,India
[3]Assistant Professor, Department of Community Medicine, Sri Manakula Vinayagar Medical College and Hospital, Pondicherry,India
[4]Assistant Professor, Department of Community Medicine, Mahatma Gandhi Medical College and Research Institute, Pondicherry,India
[5]Senior Resident, Department of Obstetrics and Gynaecology, Sri Manakula Vinayagar Medical College and Hospital, Pondicherry,India
[6]Associate Professor, Department of Pediatrics, Sri Manakula Vinayagar Medical College and Hospital, Pondicherry,India
[7]Assistant Professor, Department of Pharmacology, Sri Manakula Vinayagar Medical College and Hospital, Pondicherry,India

Corresponding Author
Dr.Priyadharshini Durairaju
Associate Professor, Department of Obstetrics and Gynaecology, Sri Manakula Vinayagar Medical College and Hospital, Pondicherry,India

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ABSTRACT

Background: Endometriosis is a chronic, estrogen-dependent condition characterized by the presence of endometrial glands and stroma outside the uterus, leading to significant pelvic pain and infertility in many women of reproductive age. Dienogest a fourth-generation progestin and gonadotropin releasing hormone (GnRH) analogues are commonly used in the treatment of endometriosis. **Objective:** To compare the efficacy of Dienogest versus GnRH analogues in the treatment of pelvic pain associated with endometriosis.**Data Sources:** PubMed and Google Scholar were systematically searched till June 2024.**Study Selection:** The meta-analysis incuded all published Randomised controlled trials that investigated the efficacy of Dienogest over GnRH analogues in the treatment of pelvic pain associated with endometriosis.**Data extraction:** Data extraction was guided by a predetermined checklist.**Analytical approach:** Using RevMan 5 software, the mean VAS score and adverse events after treatment were pooled from the selected studies. The random-effect model was used to compare the mean VAS score and the adverse events in the Dienogest and GnRH group.Data analyses were performed in July 2024.**Main Outcomes and Measures:** The primary outcome was to explore the effect of dienogest when compared to GnRH analogue in alleviating pain associated with endometriosis. The secondary outcome was to measure the adverse events in both intervention and control groups.**Results:** The initial search yielded 517 records of which 106 articles underwent full-text evaluation, which identified four articles and a total of 770 patients were included. Dienogest is equally effective as GnRH analogue in reducing the pain associated with endometriosis (Odds ratio = 0.97, 95% CI 0.52-1.78, p=0.91). An insignificant Q statistic (p >0.001) indicated the absence of heterogeneity (I^2 0%). The findings also suggested less adverse events with Dienogest when compared to GnRH analogue (Odds ratio 0.05,95%CI 0.00-0.510, p= 0.01). A significant Q statistic (p<0.00001) indicated the presence of heterogeneity I^2 =95%.**Conclusion:** This systematic review and meta-analysis demonstrated that Dienogest is equally effective with GnRH analogues in the treatment of pain associated with endometriosis with less adverse effects in dienogest than GnRH analogues. **Trail Registration:** PROSPERO Registration No CRD42024572359.

Key words: Dienogest, GnRH analogues, endometriosis associated pelvic pain

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INTRODUCTION

Endometriosis is an estrogen-dependent, chronic disease characterized by the presence of endometrial glands and stroma outside the uterus. Endometriotic disease affects about 5% of women of reproductive age[1] and is frequently associated with pelvic pain and/or infertility[2]. Ovarian endometriomas are present in up to 41% of patients with endometriosis[3,4], whereas deeply infiltrating endometriosis (DIE) has been reported in 39% of the cases of pelvic endometriosis[5] Current guidelines for the treatment of endometriosis recommend either surgical or hormonal therapies that suppress ovarian function to reduce the serum estradiol concentration and thus shrink the endometriotic lesions. Gonadotropin releasing hormone (GnRH) agonists, such as buserelin, are the principal therapeutic medications. Progestin, and estrogen progestin combinations are also used[6]. Although GnRH agonists exhibit considerable efficacy by reducing the serum estradiol concentration to postmenopausal levels, these agents are accompanied by a high incidence of hypoestrogenic symptoms, and their long-term use is associated with a substantial decrease in bone mineral density (BMD), limiting the length of time they can be used[7]. New drugs that are highly effective and that can be used over an extended period of time are thus needed. Dienogest (DNG), a progestin derived from 19-nortestosterone, has good oral bioavailability and is highly selective for progesterone receptors[8]. Because of its antiovulatory, antiproliferative activities in isolated human endometrial cells, and its inhibitory effects on the secretion of cytokines in endometriotic stromal cells[9-11], dienogest is expected to be an effective treatment for endometriosis. Good efficacy and tolerability of dienogest in patients with endometriosis have been demonstrated compared with norethisterone acetate[12].Hence, we planned to perform a meta-analysis to compare the efficacy of dienogest versus GnRH analogue in the treatment of pelvic pain associated with endometriosis.

METHODS

This study protocol was prospectively registered with PROSPERO with ID CRD42024572359 and conducted with the requirements of the reporting rules in the “Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) guidelines” and strictly complied with its specifications. Since this work is a systematic review, the heterogeneity was present within the acceptable range, meta-analysis was performed.

ELIGIBILITY CRITERIA

The criteria for the inclusion included,

- Women aged 18-45 yrs with endometriosis associated pelvic pain.
- Dienogest or GnRH analogue as intervention in any dose, duration and route.
- **Outcome Indicators:** Average VAS (Visual Analogue Scale) score and adverse events.
- Randomised controlled trials with two groups randomized to receive either dienogest or GnRH analogues.
- Studies in English language.

EXCLUSION CRITERIA

- Other study designs like Case control study, cross sectional study/observational study.
- Studies with incomplete data.
- Animal studies.

SEARCH STRATEGY

The electronic retrieval methods were adopted for the literature retrieval. A comprehensive and systematic research review using combination of Medical Subject Headings (MeSH), controlled vocabulary, and keywords was conducted through databases include PubMed and Google Scholar for studies till 2023. The keyword used were “Dienogest”, “GnRH analogues”. “Endometriosis associated pelvic pain”, “Randomised control trial”. Furthermore, a manual search of reference list of primary trials was conducted from the selected topics and relevant articles were included in the review and analysis.

STUDY SELECTION

The search results were uploaded into the online systematic review program Rayyan to conduct the study selection. A two-stage screening process were conducted for study selection. Two independent authors (D.R, P.D) performed the literature search and screened the title, abstract, and keywords of all the studies. Screening of abstract and full text was done independently by two authors (D.R, P.D) to select the studies which satisfy the eligibility criteria of our review. Any disagreements or discordances present during the entire selection process were resolved either through consensus or consultation with third author (R.M). If conflicts arose between reviewers, the fourth and fifth reviewer (J.J.F.M, P.T) moderated a discussion to come to a joint decision.

DATA EXTRACTION AND MANAGEMENT

The relevant study characteristics for the review were extracted by first and co-author independently related to outcome measure from the included studies. Data extraction was guided by a predetermined checklist with first author last name, published year, total

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sample size, gender, study design, duration of intervention, participants age, women with pelvic pain associated with endometriosis, type of intervention (Dienogest or GnRH analogues), VAS score after treatment and adverse events (Table 1 and 2).

First author (D.R) transferred the obtained data into the software Review Manager (RevMan_5.4). Data entry was double checked for correct entry by the second author (P.D) through comparison of data presented in review and included the reports.

Table 1: Characteristics of Study Population

SI. No.	Author	Year of Publication	Journal	Study setting	Study design	Blinding	Study Period	Study Population	Sampling strategy	Intervention group
1.	Yotaro T *et al.*	2016	Obstetrics and gynecology research	Hospital	Prospective cohort randomised trial	Open label	April 2009-June 2013	Adults	Randomization	Dienogest
2.	Tasuka H *et al.*	2009	Fertility and Sterility	Hospital	Randomised controlled trial	Double blinding	June 2003-February 2005	Adults	Randomization	Dienogest
3.	Maecello C *et al.*	2021	Gynecological Endocrinology	Hospital	Randomised controlled trial	Double blinding	Not mentioned	Adults	Randomization	Dienogest
4.	Strowitzki T *et al.*	2010	Human reproduction	Hospital	Randomised controlled trial	Open label	December 1998-2001	Adults	Randomization	Dienogest

Table 2: Outcome Data

SI. No.	Author	Type of comparator	Type of analysis (PP/ITT)	Intervention (Mean, SD or median (IQR))	Comparator (Mean, SD or median (IQR))	Intervention	Comparator	Pre VAS score	Post VAS score	Pre VAS score	Post VAS score	Mean change in VAS intervention	Mean VAS change in comparator
1.	Yotaro T *et al.*	Goserelin	Not mentioned	32.4 (6.6)	35.9 (6.2)	54	51	5.5	1.5	4.5	1.5	-	-
2.	Tasuka H *et al.*	Buserelin acetate	Not mentioned	33.5 (6.9)	33.8 (6.2)	137	134	7	4.9	11.9 (14.7)	43.9 (32.0)	30.2 (31.8)	27.3 (33.8)
3.	Maecello C *et al.*	Leuprolide acetate	Not mentioned	24.7 (5.3)	24. 1 (5.1)	65	81	59 (8.8)	13.3 (0.52)	59	12.2 (0.52)	-	-
4.	Strowitzki T *et al.*	Leuprolide acetate	Not mentioned	30.6 (6.2)	31 (5.8)	120	128	60.2 (24.2)	12.7 (20.3)	57.9 (21)	11.9 (16.9)	40.2 (32)	41.8 (28.6)

Outcome measure for the study

The primary outcome was to explore the effect of dienogest when compared to GnRH analogue in alleviating pain associated with endometriosis. The secondary outcome was to measure the adverse events in both intervention and control groups.

Quality Assessment

The Revised Cochrane risk-of-bias tool for randomized trials (RoB 2) was used to assess the risk of bias of the selected articles and the quality review process was monitored. Each study was categorized as follows: “low risk”, “some concerns”, or “high-risk” of bias. (Figure 1 and 2)

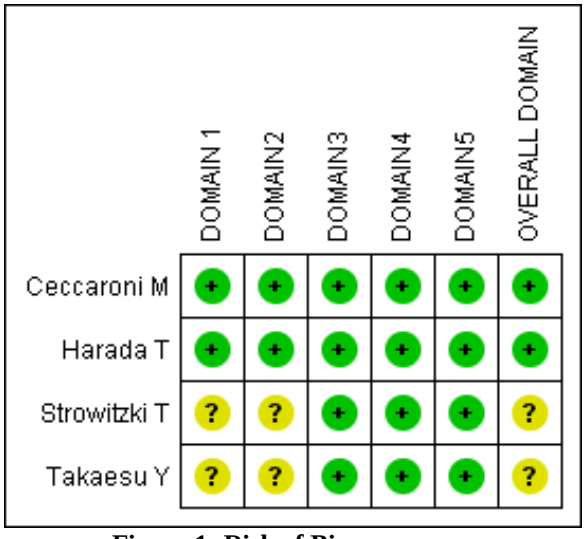

Figure 1: Risk of Bias summary

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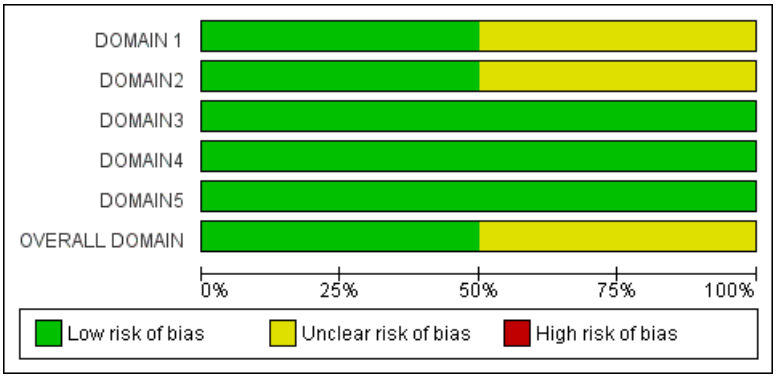

Figure2: Risk of Bias graph

STATISTICAL ANALYSIS

A comprehensive qualitative analysis was made. For quantitative Meta-analysis, the binomial data was performed using RevMan_5.4. When studies reported multiple arms in single trial, only the relevant arms were included for the analysis. Due to heterogeneity among studies, a logistic-normal-random-effect model was conducted. The 95% Confidence Interval (CI) was performed for study-specific and overall pooled prevalence, respectively. To assess the heterogeny, I^2 statistics was used. Significant heterogeny was considered if p-value <0.05 or I^2>50% among the studies.

RESULTS

STUDY SELECTION AND CHARACTERISTICS

A total of 498 studies were initially retrieved following the removal of duplicates. On screening 392 studies were deemed irrelevant to our review. The remaining 106 were assessed for eligibility. Of those, four studies met the inclusion criteria and were ultimately included for the qualitative and quantitative analysis**.** Figure 3 illustrates **t**he PRISMA flowchart for the study selection.

When using Cochrane risk-of-bias tool, two studies had low risk of bias, and two studies had some concerns**.** The major limitation was small sample size in two studies. Baseline characteristics were found to be similar in both intervention and control groups in all studies. In all four studies, Dienogest was equally effective to GnRH analogue in relieving the pain symptoms, but GnRH analogue group reported increased adverse events than dienogest which was statistically significant.

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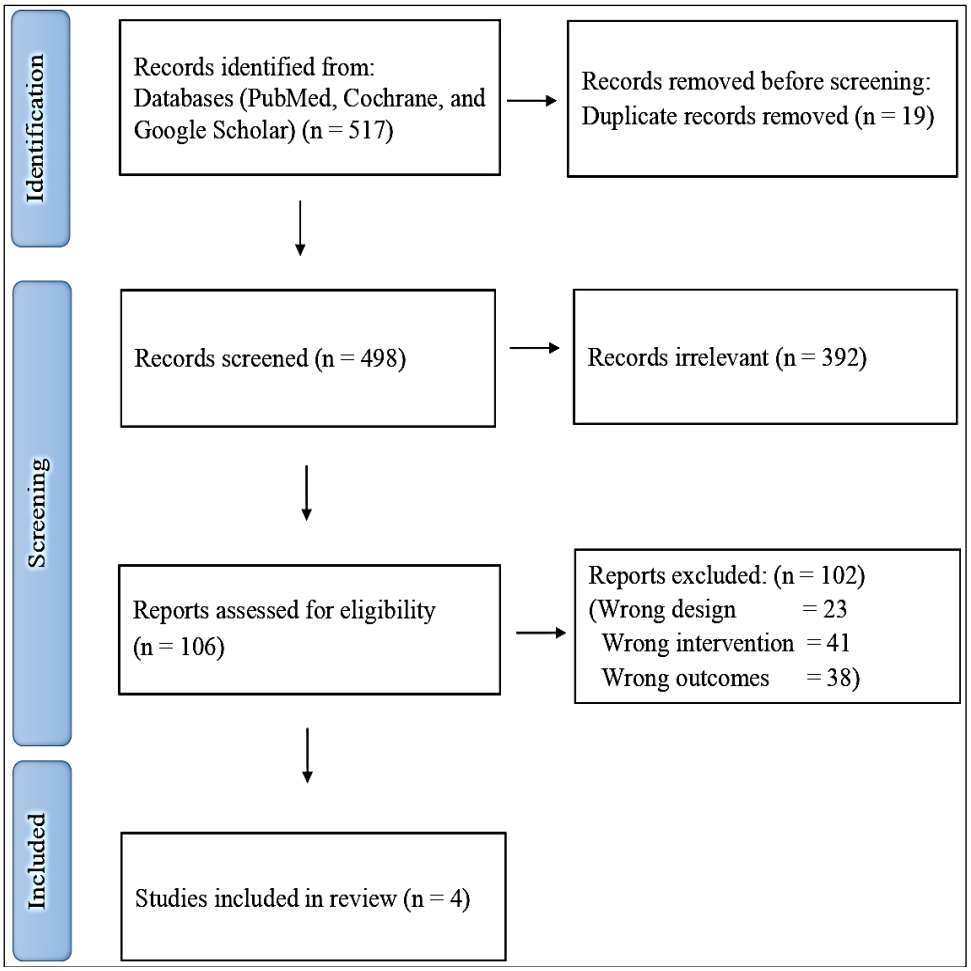

Figure 3: PRISMA flow diagram of the study selection process

CHARACTERISTICS OF THE STUDY POPULATION

From all four studies included, a total of 376 patients were in the intervention group and 394 patients were in the control group. The mean age for the overall cohorts included in this study ranged from 24.1years to 35.9 years. All the studies used dienogest for intervention group and GnRH for control group. The duration of the study ranged from 2 years to 4 years.

METHODOLOGICAL QUALITY OF THE INCLUDED STUDIES

The included four studies of the final review were all randomised controlled trials with Dienogest as one the intervention and GnRH in the comparator group. These articles were published between 2009 to 2021 done in the hospital setting.

PAIN RELIEF AFTER TREATMENT

A meta-analysis of 4 eligible comparative studies involving 376 subjects exposed to Dienogest and 394 subjects exposed to GnRH analogues demonstratesDienogest is equally effective as GnRH analogue in reducing the pain associated with endometriosis (Odds ratio (OR) = 0.97, 95% CI 0.52-1.78, p=0.91), heterogeneity (I^2 =0%), the pooled OR was calculated using the random effect model as shown in Figure 4. An insignificant Q statistic (p >0.001) indicated the absence of heterogeneity.

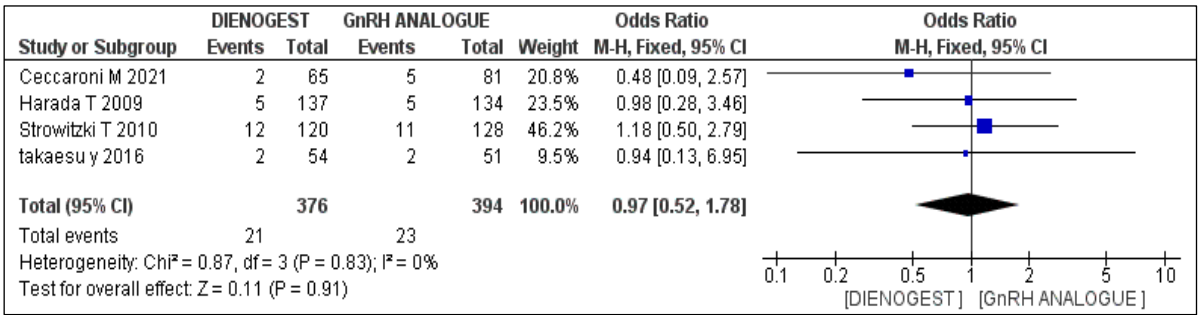

Figure 4: Pain relief in Dienogest group versus GnRH group

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TREATMENT RELATED ADVERSE EVENTS

A meta-analysis of 4 eligible comparative studies involving 376 subjects exposed to Dienogest and 394 subjects exposed to GnRH analogues demonstrates less adverse events in Dienogest when compared to GnRH analogue. (Odds ratio 0.05, 95%CI 0.00-0.510, p= 0.01), heterogenity (I2= 95%) as shown in Figure 5.

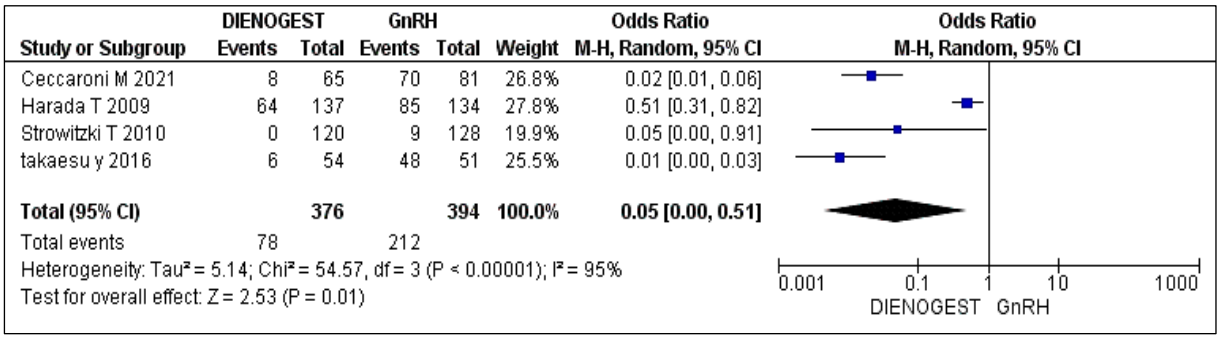

Figure 5: Adverse events in Dienogest group and GnRH group

DISCUSSION

Endometriosis is an estrogen-dependent chronic inflammatory disease affecting 6-10% of women of childbearing age[17].Endometriosis is associated with infertility and a variable degree of pelvic pain[18].Patients usually present with chronic pelvic pain, dysmenorrhea, dyspareunia, and infertility. Endometriosis-related pain has an adverse effect on the quality of life of these patients[19]. It is recommended to offer women hormone treatment (combined hormonal contraceptives, progestogens, GnRH agonists or GnRH antagonists) as one of the options to reduce endometriosis-associated pain.Women may be offered NSAIDs or other analgesics (either alone or in combination with other treatments) to reduce endometriosis-associated pain[20].

Dienogest is a new generation of progestin carrying the pharmacological specialties of 19-norprogestin and progesterone derivatives. It has been shown that dienogest has strong progestogen, androgenic, mineralocorticoid, and glucocorticoid effects[21]. GnRH agonist have proven to be very efficient in treating endometriosis but long-term usage in women may lead to calcium loss from bone as a result of hypoestrogenism[22]. In recent years significant advances have been made in the treatment of endometriosis, and drugs remain the primary treatment option for women of child bearing age. However, there is no agreement on which drugs are most effective and tolerated for the treatment of endometriosis. Hence this study was conducted to improve the choice of medications for patients.

In the present study all four Randomised controlled trials[13, 14, 15, 16] included in this meta-analysis, showed that dienogest was as effective as GnRH analogues for effective pain relief in pelvic pain associated with endometriosis (Odds ratio = 0.97, 95% CI 0.52-1.78, p=0.91), heterogeneity (I^2 =0%). A study conducted by Dai Y in 2021 reported that Dienogest is more effective in pain relief and cost saving compared to GnRH analogues[23]. In the present study, all four randomised control trials included in this meta-analysis showed less adverse events with dienogest when compared to GnRH analogues. (Odds ratio 0.05, 95%CI 0.00-0.510, p= 0.01), heterogenity (I2= 95%). Hence rates of discontinuation due to adverse events will be less with Dienogest compared to GnRH analogues. Similar results was observed in the study conducted by Schindler A in 2011[24].

From the present study it is evident that Dienogest is equally effective in the treatment of pelvic pain associated with endometriosis with less adverse effects. Hence, Dienogest can be considered as a better alternative to GnRH analogues for pain relief while offering advantages in safety and tolerability. There were some limitations in the study, like number of studies were limited and in two studies there were some concerns in randomisation.

CONCLUSION

The results of our meta-analysis suggest that Dienogest is comparable to GnRH analogues in the treatment of pain associated with endometriosis with less adverse effects in Dienogestthatn GnRH analogues. Further larger multi-centered longitudinal studies can help in predicting the effective dosage and duration of treatment for endometriosis associated pelvic pain.

AUTHOR CONTRIBUTIONS

Rajendran D and Durairaju P had a full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Mohan R and Mary JJF analysed and did data interpretation. Sulaiman SP, Tamilarasan P, and Mohan R contributed equally. Dr Sanjy P was the senior for the study.

CONCEPT AND DESIGN: Rajendran D and Durairaju P.

ACQUISITION OF DATA: Rajendran D and Durairaju P.

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ANALYSIS, OR INTERPRETATION OF DATA: Mohan R, Mary JJF.

DRAFTING OF THE MANUSCRIPT: Rajendran D and Durairaju P.

CRITICAL REVISION OF THE MANUSCRIPT FOR IMPORTANT INTELLECTUAL CONTENT: Sanjay P.

STATISTICAL ANALYSIS: Mohan R, Mary JJF.

ADMINISTRATIVE, TECHNICAL, OR MATERIAL SUPPORT: Sanjay P.

CONFLICT OF INTEREST DISCLOSURES: No disclosures or conflicts of interest were reported.

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