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Does caffeine reduce methotrexate intolerance in patients with rheumatoid arthritis: a randomized controlled study

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Abstract

Background: Intolerance to MTX is the most common cause of non-compliance that leads to poor disease control. Treatment is usually discontinued due to intolerance which interferes with compliance of the patient to long-term treatment. Caffeine causes most of its biological effects via antagonizing all types of adenosine receptors (ARs). Our aim was to investigate the effect of caffeine intake on reducing symptoms of MTX intolerance in patients with RA.

Methods: Ninety patients were diagnosed as RA with MTX intolerance divided into 2 groups. Sixty patients were prescribed caffeine or dark chocolate. Control group included 30 patients who will continue MTX regimen without addition of any extra caffeine.

Results: Group A (caffeine group): There was no statistically significant difference between patients and controls at the start of the study. There was statistically significant decrease in methotrexate intolerance severity score (MISS) all over the study period ($P = 0.001$), and also MISS was statistically significantly lower in each follow-up time when compared with time 0 ($P = 0.001$).

Group B (control group): There was statistically significant increase in MISS all over the study period ($P = 0.017$); also, MISS was statistically significantly higher in follow-up time 2 and time 3 when compared with time 0 ($P = 0.033$). We found that after 3 months, 80% of group A patients showed complete relief, 6.7% showed partial relief, 10% showed minimal relief, and 3.3% got worse.

Conclusion: Adding caffeine to management regimen can reduce the symptoms of MTX intolerance in RA patients. Caffeine relieved the symptoms of MTX intolerance in 80% of RA patients after 3 months of adding caffeine to management regimen.

Keywords: Rheumatoid arthritis (RA), Caffeine, Methotrexate intolerance

Background

Rheumatoid arthritis (RA) is an autoimmune chronic inflammatory arthritis affecting about 5 per 1000 of the adult general population worldwide with disease onset at any age (peak at 55 years) and 2 to 3 times higher incidence in

women than men [1]. Despite the development of many types of therapies for RA in recent years, methotrexate (MTX) has remained anchor disease-modifying antirheumatic drugs (DMARD) for most patients since the late 1980s because of its potent efficacy; however, despite its long-term and widespread use for RA, the precise mechanism of this drug remains unknown [2]. Nearly 20–30% of RA patients stopped MTX because of MTX intolerance within the first year of therapy [3]. Intolerance to MTX is the most common cause of non-compliance leading to poor

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disease control. MTX intolerance symptoms may be categorized as:

1. Gastrointestinal symptoms including nausea, abdominal cramps, bloating, pain, discomfort, heaviness, acidity, epigastric distress, loose motions, or constipation [4]
2. Behavioral symptoms including anticipatory symptoms such as anxiety, aversion to MTX name, seeing or thinking of ampule, depression, aversion to food, unpleasant taste and odors, insomnia, headaches, and difficulty in concentration
3. Nonspecific symptoms including fatigue, loss of appetite, the whole body feeling hot, and burning in the chest [5]

The adenosine signaling pathway is the leading hypothesis to explain the efficacy of methotrexate in RA patients. Adenosine can be formed intracellularly from ATP and exported from the cell, but the majority of adenosine is formed extracellularly by sequential dephosphorylation of ATP to adenosine in the extracellular space [6].

Methylxanthines (e.g., caffeine, cocoa, and theophylline) act as adenosine receptor antagonists in humans. MTX acts by increasing extracellular adenosine. This means that caffeine causes most of its biological effects via antagonizing all types of adenosine receptors (ARs) [7]. Methylxanthines reverse MTX effect by preventing the nucleoside from acting on receptors [4].

Our aim was to investigate the effect of caffeine intake on reducing symptoms of MTX intolerance in patients with RA.

Methods

This is a prospective, randomized controlled study conducted at Aswan University Hospital, Aswan, Egypt from May 2018 till May 2019. Ninety patients diagnosed as RA according to 2010 American College of Rheumatology/European League Against Rheumatism (ACR-EULAR) classification criteria for RA [8] attending the outpatient clinic were enrolled in the study. All of patients experienced moderate to severe MTX intolerance according to methotrexate intolerance severity score (MISS). Written informed consent was obtained from all study participants. Study was approved by Ethical Medical Committee of Faculty of Medicine, Aswan University, Aswan, Egypt according to the guidelines of the Helsinki Declaration.

Patients less than 18 years, patients drinking > 4 cups caffeine/day (> 548 mg/day as each cup contains 137 mg according to the US Department of Agriculture food) [9, 10], patients with renal or hepatic impairment, and pregnant women were excluded from the study.

The disease activity in RA patients was assessed by the 28 joint count Disease Activity Score (DAS 28) using the number of swollen and tender joints, erythrocyte sedimentation rate (ESR), and patient's global status, and pain was evaluated by the visual analog scale (VAS) range from 0 to 100 mm [11].

Group A: Sixty patients were prescribed caffeine (coffee or dark chocolate) as an antidote to MTX intolerance according to the schedule used in Malaviya's study and was described below [4].

Coffee schedule for non-coffee-drinking patients: One to one and half teaspoon of powdered "instant coffee" (containing ~ 30–45 mg caffeine) prepared in 160 to 200 ml water (taken with or without milk, with or without sugar) synchronized with MTX weekly dose. Regimen of coffee was prescribed three times during MTX weekly dose as follow: the first dose to be taken with breakfast, the second in the evening 1–3 h before MTX dose, and the last dose at the next day morning. This amount of coffee would be equivalent to 90 to 135 mg of caffeine over 24 h.

For coffee-drinking patients: the above schedule was added to the cups taken by the patient on the day of MTX administration.

Dark chocolate: Patients who did not like coffee or dark chocolate will be advised as follows: to take "four squares" (40 gm) of the most popular brand of "dark chocolate," i.e., if MTX intolerance persisted, they will be free to take another 40 g of chocolate after 8–12 h. This amount would be equivalent to 88 to 176 mg of caffeine over 24 h [4].

Group (B): The control group included 30 patients who will continue MTX regimen without addition of any extra caffeine.

Study protocol

The patient characteristics such as age, gender, the duration of MTX treatment, the period after which MTX intolerance began, and dose/route of MTX at which symptoms of intolerance appeared were documented. The methotrexate intolerance severity score (MISS) was evaluated at base line before initiation of therapy, then at the next 3 months consecutively. The details of the various medications and other measures used for the control of symptoms of MTX-intolerance were also recorded. These included antiemetics, antacids, proton-pump inhibitors, sugar candy, and plain sugar. Both groups were prescribed with folic acid supplements in a dose of one tablet (500 mcg) each day except on the day of injection.

MTX intolerance severity score

The initial MISS questionnaire contained 16 items divided into 5 domains, including abdominal pain

(stomach ache), nausea, vomiting, oral pain (sore mouth), and behavioral symptoms. The first 4 domains contained 3 items each, related to adverse effects after MTX intake as well as anticipatory and associative adverse effects. The fifth domain, on behavioral symptoms, included restlessness, crying, irritability, and refusal of MTX. On each item, a patient could score 0 (no symptoms), 1 point (mild symptoms), 2 points (moderate symptoms), or 3 points (severe symptoms). MTX intolerance was defined as ≥ 6 points, including at least one anticipatory, associative, or behavioral symptom [12]. The MTX intolerance was classified into: (i) "Minimal" or "Mild," if patients were able to manage it by themselves in the various ways including taking sugar candy or plain sugar, adjusting the MTX timing; (ii) moderate, when the patients required antiemetics/antacids, dose/route of adjustment (including shifting from oral to parenteral route) in addition to antiemetics and antacids; (iii) "Severe," if the patient was inclined to discontinue MTX despite these measures; MISS was repeated at each follow-up visit [4].

Grading of the response to caffeine

- 1) Complete relief: if symptoms of MTX-intolerance improved so that the anti-emetic and other drugs for its control were discontinued.
- 2) Partial relief: if the symptoms were better, but antiemetics/antacids were still needed.
- 3) Minimal relief: if there was no improvement of symptoms.
- 4) Worse: if caffeine caused similar aversion as did MTX [4].

Statistical methods

All analyses were performed using the SPSS software (version 24.0; SPSS Inc., Chicago, IL). *P* values of ≤ 0.05 will be deemed to indicate statistical significance. The pretreatment and posttreatment outcomes were compared by using the paired *t* test for quantitative data and the Mc Nemar test for qualitative data. The two groups were compared by using an independent samples *t* test for quantitative data and the 2 tests for qualitative data. Screening for extreme values in quantitative variables was done by using independent student *t* test and repeated measures ANOVA test with Bonferroni post hoc test. Discrete and categorical variables were screened by using frequency distribution and Fisher's exact test.

Results

Ninety patients were enrolled in the current study (Fig. 1).

Our results showed that the mean age was 48.6 ± 10.6 years in group A (caffeine group) in comparison to 45.6 ± 12.7 in group B (control group). The percentage of male to female was equal in both groups. Twenty percent of group A has medical history of hypertension versus 10% in group B. Four patients were diabetic in group A in comparison to two patients in group B. There was no statistically significant difference between the two studied groups regarding these variables (*P* values 0.324, 1.000, 0.402 respectively) (Table 1).

As regards DAS-28, mean \pm SD was 4.28 ± 1.62 and 4.97 ± 1.4 for groups A and B, respectively, with no significant difference between the two groups during the follow-up period (*P* value 0.476).

MTX prescription data

The mean duration of MTX treatment was 38.3 ± 48.5 and 30.5 ± 32.0 months in groups A and B, respectively. The mean duration since the onset of MTX intolerance was 19.5 ± 18.5 for group A and 18.3 ± 17.7 months for group B. The mean dose of MTX in groups A and B were 15.4 ± 4.3 and 14.7 ± 3.9 mg per week, respectively. Most patients in both groups received their doses of MTX subcutaneously (93.3%, 86.7%). There was no statistically significant difference between the two studied groups regarding these variables (*P* values 0.467, 0.798, 0.345, and 0.671, respectively) (Table 2).

MTX intolerance severity score

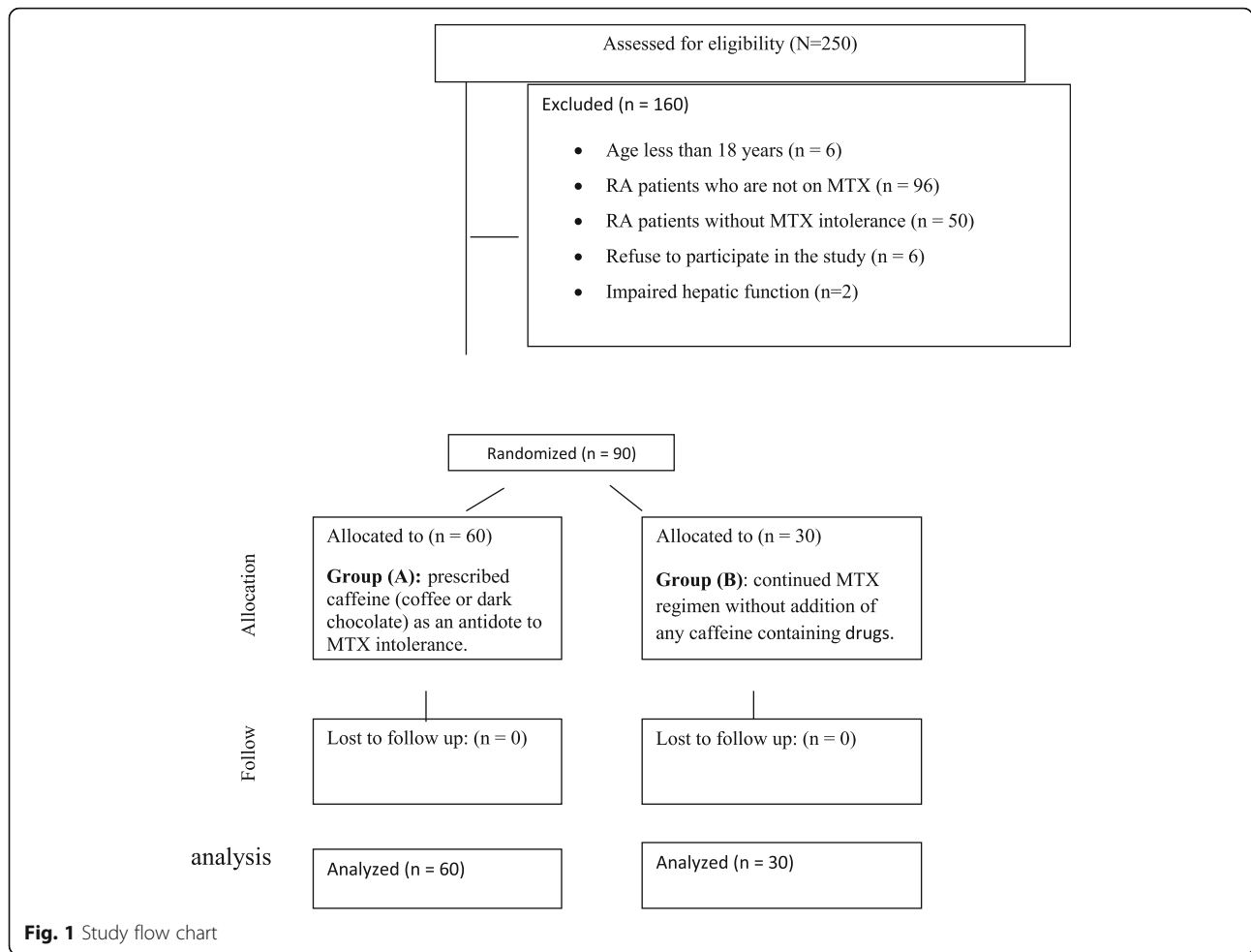
Group A: There was statistically significant decrease in the mean MISS score all over the study period (*P* = 0.001) except for time 0 where *P* value was 0.202, and the mean MISS score was statistically significantly lower in each follow-up time when compared with time 0 (*P* = 0.001).

Group B: There was statistically significant increase in MISS all over the study period (*P* = 0.017), and also MISS was statistically significantly higher in follow-up time 2 and time 3 when compared with time 0 (*P* = 0.033) (Fig. 2, Table 3).

Figure 3 shows the effect of caffeine on MTX intolerance in group A all over the study period. We found that at time 3, 80% of patients showed complete relief, 6.7% showed partial relief, 10% showed minimal relief, and 3.3% worsen.

Discussion

Caffeine is a known antagonist of adenosine receptor. Inhibition of these receptors in the CNS may thus improve MTX intolerance. Hypothetically, this could also reduce the noxious effects of MTX on inflammation as adenosine receptors are involved in its therapeutic action [13].



The main finding of this study was that adding caffeine to management regimen can reduce the symptoms of severe MTX intolerance in RA patients. Caffeine relieved the symptoms of severe MTX intolerance in 80% of patients after 3 months so much that the antiemetic and other drugs were discontinued. While 6.7% showed partial improvement of symptoms during the same period but the antiemetic and other drugs were still needed, 10% showed

minimal improvement of symptoms, and 3.3% reported worsening of symptoms and stopped caffeine.

Our study came in accordance with a study on 120 RA patients whom had moderate or severe MTX intolerance when added caffeine; 55% had complete relief of symptoms and were able to continue taking the MTX, while 13.3% had partial improvement and continued taking MTX with antiemetics; 7.5% were minimally better but were somehow managing, and 10 % were complete

Table 1 Demographic data of two studied groups

Demographic variable		Group A (n = 60)	Group B (n = 30)	P value
Age	Mean ± SD	48.6 ± 10.6	45.6 ± 12.7	0.324
	Range	26–60	18–65	
Gender no (%)	Male	8 (13.3%)	4 (13.3%)	1.000
	Female	52 (86.7%)	26 (86.7%)	
Medical history no (%)	None	44 (73.3%)	26 (86.7%)	0.402
	Hypertension	12 (20%)	3 (10%)	
	Diabetes	4 (6.7%)	2 (3.3%)	

Table 2 Comparison between the two studied groups regarding MTX prescription data

Demographic variable		Group A (n = 60)	Group B (n = 30)	P value
MTX duration (month)	Mean \pm SD	38.3 \pm 48.5	30.5 \pm 32.0	0.467
	Range	4–168	1–120	
MTX intolerance duration (month)	Mean \pm SD	19.5 \pm 18.5	18.3 \pm 17.7	0.798
	Range	3–60	1–60	
Dose of MTX(mg)	Mean \pm SD	15.4 \pm 4.3	14.7 \pm 3.9	0.345
	Range	12.5–17.5	12.5–17.5	
Route of administration n (%)	IM	4 (6.7%)	4 (13.3%)	0.671
	SC	56 (93.3%)	26 (86.7%)	
Medications to control intolerance n (%)	None	12 (20%)	6 (20%)	0.532
	Pantoprazole	48 (80%)	21 (70%)	
	Antiemetics	0 (0%)	1 (3.3%)	
	Pantoprazole + antiemetics	0 (0%)	2 (6.7%)	

caffeine failure without any relief. The significant relief with a schedule of coffee intake synchronized with MTX has urged the recommendation that adult patients with RA and MTX intolerance should drink “a few cups more coffee” on the day of MTX administration [4].

Another study done included a total of 410 patients; 396 (96.58%) with RA, 4 (0.97%) with spondyloarthritis and 10 (1.21%) others (undifferentiated connective tissue diseases, systemic lupus erythematosus Sjogren’s). The severity of the intolerance was measured on a score 0–100 numeric. Of the 410 patients, 212 (51.7%) had minimal MTX intolerance so that no intervention was required. One hundred ninety-eight (48.29%) patients had moderate-severe MTX intolerance and was advised to take strong coffee on the day of MTX-dose as follows: two cups early in the morning, another two cups 2–3 h before the dose of MTX taken late in the evening. A 3rd dose of two cups was repeated the next morning with breakfast. They found that 15.15% of patients had complete relief, 7.57% had 70–95% relief of symptoms, and 44.94% had 10–60% relief of symptoms [14].

A study was performed on 115 RA patients who had moderate or severe MTX intolerance. Among these, 52 (45.2%) had complete relief of symptoms with the addition of caffeine; 17 (14.8%) had partial improvement and continued taking MTX but only with antiemetic; 14 (12.2%) were minimally better but were somewhat managing; 14 (12.2%) did not get any relief and discontinued MTX [15].

Another study published in 2017, authors concluded that caffeine relieved the symptoms of MTX intolerance in 56% and gave partial relief in another 13% of the patients [4].

Some authors suggested that caffeine may interfere with MTX efficacy. Neshet et al. conducted a study on 39 RA patients; they were divided in 3 groups; each group had different amount of caffeine intake (low < 120 mg/day, medium 120–180 mg/day, and high > 180 mg/day). They concluded that caffeine, in daily amounts > 180 mg, interferes with the efficacy of MTX in patients with RA, when compared with patients consuming < 120 mg/day [16]. Another study published in 2006 on 264 RA patients, authors

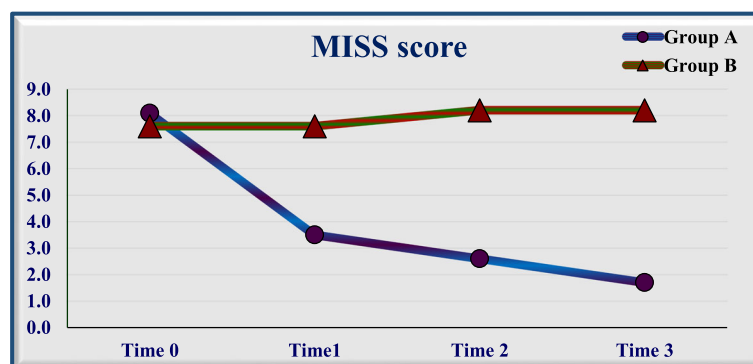
**Fig. 2** Comparison between the two study groups regarding MISS score

Table 3 Comparison between the two studied groups regarding MISS score

MISS score		Group A (n = 60)	Group B (n = 30)	P
Time 0 (baseline)	Mean ± SD	8.1 ± 1.5	7.6 ± 1.3	0.202
	Range	6–12	6–10	
Time 1 (after 1 month)	Mean ± SD	3.5 ± 7.9	7.9 ± 1.3	0.001*
	Range	0–9	6–11	
Time 2 (after 2 months)	Mean ± SD	2.6 ± 2.5	8.2 ± 1.5	0.001*
	Range	0–9	6–12	
Time3 (after 3 months)	Mean ± SD	1.7 ± 2.3	8.2 ± 1.5	0.001*
	Range	0–9	6–12	
P0		0.001*	0.017*	
P1		0.001*	0.053	
P2		0.001*	0.033*	
P3		0.001*	0.033*	

P P value for independent student t test for comparison between the two studied groups, P0 P value for repeated measures ANOVA test for comparison in between the same group, P1 P value for Bonferroni post hoc test between time 0 and time 1 in the same group, P2 P value for Bonferroni post hoc test between time 0 and time 2 in the same group, P3 P value for Bonferroni post hoc test between time 0 and time 3 in the same group

conclude that high caffeine consumption does not affect methotrexate efficacy, compared with low and moderate caffeine consumption [5]. This is in accordance to our study as we found no significant difference between the two groups during follow-up period which means that this caffeine dose did not interfere with MTX efficacy.

Our study has some advantages. First, we used natural coffee in the intervention group, and this augmented patient satisfaction due to avoidance of multiple chemicals that was needed to control MTX intolerance. Second, in contrast to previous studies which have included all degrees of MTX intolerance, our study included moderate to severe MTX intolerance. This allows precise evaluation and decreases bias. Third, we used MISS score for evaluation and

follow-up of patients during treatment period which allowed to provide greater precision, which translates to greater statistical power to detect response to treatment. Lastly, the dose of caffeine was calculated and prepared by the observer which achieved more precise and accurate dose of caffeine.

There were some limitations in the study. First, sample size was small and larger studies are still needed to ensure replicability. Second, MTX intolerance was assessed subjectively using the available MISS with no available another objective tool that could provide more accurate information. Lastly, to avoid the limitation of inability to be sure of patient’s adherence, a suggestion that could help in future similar studies is that to try to follow adherence of patients to coffee drinking using diaries in which

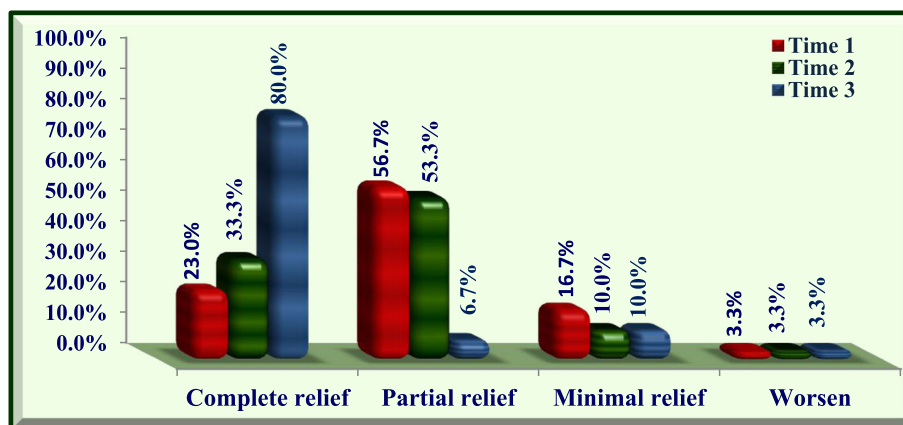


Fig. 3 Distribution of the effect of caffeine on MTX intolerance in caffeine group all over the study period

patients record their intake, and this can be reviewed by the authors during the follow-up visits which will give a feedback about adherence.

Conclusion

Adding caffeine to management regimen can reduce the symptoms of severe MTX intolerance in RA patients. Caffeine relieved the symptoms of severe MTX intolerance in 80% of patients after 3 months of adding caffeine to management regimen.

Abbreviations

RA: Rheumatoid arthritis; MTX: Methotrexate; ARs: Adenosine receptors; MISS: Methotrexate Intolerance Severity Score

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Not applicable.

Authors' contributions

Dr. FE, AF, and RL shared the conceptualization, study design, clinical work, investigations, formal analysis, and revised the written paper. Prof. NF, SG, and AA shared also conceptualization, the study design, writing the paper, conducting the results and formal analysis. All authors have read and approved the manuscript. Dr. SG was responsible for paper submission.

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Availability of data and materials

All data and materials are available on request.

Ethics approval and consent to participate

Study was approved by Ethical Medical Committee of Faculty of Medicine, Aswan University according to the guidelines of the Helsinki Declaration (Aswu/192/12/17). All patients gave informed written consent.

Consent for publication

All participants of the study approve the submission.

Competing interests

All authors declare no conflict of interest.

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