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Traditional Dry Cupping Therapy Versus Medroxyprogesterone Acetate in the Treatment of Idiopathic Menorrhagia: A Randomized Controlled Trial

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Abstract

Background: Dry cupping has been used as a treatment for abnormal uterine bleeding in Iranian traditional medicine.
Objectives: The present study aimed at evaluating the usefulness of dry cupping on excessive menstrual blood loss in menorrhagia with a well- validated menstrual pictogram compared to medroxyprogesterone acetate.
Methods: A total of 162 women with menorrhagia were enrolled in this prospective, randomized, controlled trial in Iran from 2015 to 2016. Written informed consent was obtained, then, patients were randomly allocated into dry cupping (three sessions of interrupted and kinetic dry cupping during menstrual bleeding) or medroxyprogesterone acetate (10 mg/day throughout the luteal period) groups using a random number sequence. The number of bleeding days and objective estimation of menstrual blood loss using a pictorial blood loss assessment chart (PBAC) were recorded before the intervention and at specific intervals (one and 3-months post-intervention).
Results: At one and 3-months, PBAC scores were significantly lower in women treated with cupping compared with women treated with medroxyprogesterone acetate. These reductions in PBAC score were 214.9 mL with 95% CI (120.5 to 309.2) greater than medroxyprogesterone acetate at one month and 237.3 with 95% CI (143.0 to 331.7) at 3- month follow- up period. Reduction in the number of bleeding days in the cupping group for almost one day was better than the control groups at one and 3-months follow- up (Mean difference:-1.03, 95% CI (-1.78 to -0.26), P = 0.007).
Conclusions: Dry cupping is an effective treatment in reducing the intensity of bleeding during the menstrual period compared to medroxyprogesterone acetate.

Keywords: Complementary Medicine, Cupping, Metrorrhagia, Traditional Medicine, Uterine Hemorrhage

1. Background

One of the most common reasons for female patients to seek health care is Abnormal Uterine Bleeding (AUB), which is irregular and more intense than previous periodic menstrual bleeding (1). About 20% of girls and women experience AUB disorder in their lifetime (2). AUB is commonly found in women of childbearing age and includes 20% of all gynecological visits (3).

Severe bleeding causes physical weakness and anemia and reduces educational, social, and family efficiency (2). From psychological perspective, severe bleeding is associated with mental confusion and various concerns (such as the possibility of incurable diseases, disorganization of ceremonies and religious rites of a person, restrictions on sexual relations with a partner, the side effects of chemical drugs prescribed, and lack of responsiveness to the classic remedies) (4). Even in 10% of cases of failure to respond to current treatments, the physician and patient are convinced to use hysterectomy, which may cause some physical and mental symptoms, such as depression and obesity (5).

Given the lack of selective treatment options, side effects, drug interactions, and limitations of current

treatments, presently, the patients with AUB not only benefit from current treatments such as hormone therapy and combination of prostaglandin inhibitors nonsteroidal anti-inflammatory drugs, oral contraceptive, and gonadotropin agonists, but also they can use the whole range of complementary and alternative medicines (1, 2).

Dry cupping is a simple, clear, and well-known procedure in the manual methods of Persian medicine (6). During cupping therapy based on the type of disease, creating suction and negative pressure on specific areas results in a therapeutic effect. Several studies have recommended cupping therapy for the treatment of many disorders (7, 8). Cupping therapy has been introduced as a method of vaginal bleeding management in Persian traditional medicine. However, there is no documented study in this area. Due to the limitations and side effects of the drugs used in the management of AUB on one hand, and the simplicity, speed of impact, lack of severe side effects, not interacting with other therapies of dry cupping on the other hand, it is necessary to conduct a study to demonstrate the effectiveness of this treatment as a novel method (9-12). The aim of this study was to evaluate the usefulness of dry cupping on excessive menstrual blood loss in menorrhagia, with a well- validated menstrual pictogram compared to medroxyprogesterone acetate.

2. Methods

2.1. Participants and Study Design

This was a prospective, randomized, placebo, controlled study, performed on women with AUB in accordance with consolidated standards of reporting trials (CONSORT) guidelines (13).This study was conducted at the Ruin Tan Arash hospital, Tehran, Iran, during November 11, 2015 and March19, 2016. Ruin Tan Arash hospital is a general women's hospital located in Tehranpars, an Eastern suburb of Tehran in Iran. It is an educational, research and treatment center for gynecology and obstetrics.

The participants were selected according to the defined inclusion criteria: 20 to 50 years old, no history of chest surgery in the last three months, no drug abuse in the past six months, no history of coagulation disorders, no underlying diseases, no infectious skin lesions and scarring in the chest, no rib fracture history, not pregnant or planning a pregnancy during the study period, and endometrial thickness less than 12 mm. Exclusion criteria were as follow: history of significant medical problems (coagulopathies, diabetes mellitus, chronic inflammatory disease, and thyroid dysfunctions), BMI < 18 kg/m^2, allergies and skin sensitivity, a history of endometrial abnormalities (such as hyperplasia), cervical carcinoma, uterine or ovary malignancy, and submucosal or intramural fibroids more than 5 cm. Patients were advised to refrain from taking mefenamic acid, tranexamic acid, any hormonal therapy, herbal medicine, and medicinal herb during the study.

The study was performed in accordance with the declaration of Helsinki (14) and was approved by Tehran University of Medical Sciences clinical research ethics board. Written informed consent was obtained from the patients before any study-related tests were done. The study was registered in Iranian registry of clinical Trial (www.IRCT.ir) (IRCT2016052528080N1).

After obtaining written informed consent, patients were randomly allocated into dry cupping or medroxyprogesterone acetate using a random number sequence. Randomization was done by using ALEA, an online randomization program, managed by the clinical research unit in the Academic Medical Centre in Amsterdam, with the use of permuted blocks with a random block size of six patients per block. Allocation concealment was maintained by sequentially numbered opaque sealed envelopes until the patient was screened and approved for inclusion. Trial's epidemiologist, who was not involved in the selection and allocation of patients, prepared, coded, and sealed the opaque envelopes.

2.2. Intervention in Group A (Dry Cupping)

Patients allocated into the cupping group received 3 sessions of interrupted and kinetic dry cupping during menstrual bleeding. Cupping was performed by the study nurses, who were trained in cupping and regularly performed cupping in a clinical setting. The cupping procedure was performed as follows: The patient laid down on the massage bed with her upper torso bared. Three glass cups with a size of 6 cm (external diameter) was applied below and above each breast with an interval of half an hour for 10 minutes. The vacuum was created with 3 double-walled glass cups, with a size of 6 cm (external diameter) and were held inverted over an open flame to heat the air inside, after which the glass cups were placed below and above each breast at an interval of half an hour for 10 minutes (One up and two down). As the air inside the cups cooled, vacuums were created, drawing up the skin within each cup.

2.3. Intervention in Group B (Medroxyprogesterone Acetate)

Throughout the luteal period, each participant self-administered an oral medroxyprogesterone acetate tablet (10 mg/day; IRANHORMONE, Tehran, Iran).

2.4. Outcomes

At the time of randomization, complete obstetric and medical histories were reported in the case report file. The menstrual history included the duration of symptoms, number of bleeding days, subjective assessment of menstrual blood loss, the presence of dysmenorrhea, and the passage of clots/flooding during menses. The primary outcome was menstrual blood loss that was assessed with pictorial blood loss assessment chart (PBAC) (15, 16). The PBAC score was calculated by assigning a score of 1, 5, or 20, respectively, to a lightly, moderately, or fully soiled sanitary pad, and a score of 1 or 5, respectively, for the passage of small or large clots. The women were instructed to insert a mark in the appropriate box at the time each towel and/or tampon was discarded, and if sufficient, they were counted in groups of five. To assess the effect of treatments on menstrual blood loss, patients were visited monthly for three months during the treatment period and were asked to complete a new menstrual chart every month before each follow-up, when a gynecological examination and evaluation of their PABC score was performed and any adverse reaction was observed.

2.5. Sample Size

PBAC score was considered as the primary outcome for sample size calculation. A repeated measures design with one between factor (intervention groups) and one within factor (times of recording) requires 77 participants per intervention group for a total of 154 participants to achieve 80% power to detect average differences of 80 mL in PBAC score in 2 treatment groups (an effect size of 0.23). The standard deviation of PBAC in each treatment group was assumed to be 175 mL and equal in the 2 treatment groups. Also, this estimated total sample size achieved 91% power to test within factor and interaction of factors, when an effect size of 0.27 was assumed. The expected rate of dropout was considered at 5%, so the final sample size was estimated to be 81 participants per treatment group. All the aforementioned calculations assumed 0.05 level of significance.

2.6. Statistical Analysis

Categorical and continuous variables were summarized as proportions and mean $\pm$ standard deviation, respectively. Data were analyzed using intention to treat methods. To evaluate the quality of randomization and balance of characteristics of participants before intervention in the two treatment groups, baseline measures for quantitative and qualitative variables were compared using student's t test and chi square test, respectively. PBAC score 1 and 3 months after intervention was considered as outcome, and the effects of treatment groups, time of recording and interaction of treatments $\times$ times were evaluated using flexible statistical mixed model. Also, for better presentation of the magnitude of reduction in PBAC score and the differences between the treatment groups after intervention, change from baseline was calculated for 1 and 3 months after intervention. Moreover, the effect of treatment, time, and interaction was evaluated on change score of PBAC. This procedure was repeated for number of bleeding days and number of pads consumption. Size of the estimated effects between the treatments was reported with 95% confidence intervals. All statistical analyses were done using STATA Package (StataCorp, College Station, Texas, USA), Version 13, and P-value of < 0.05 was considered statistically significant.

3. Results

During November 11, 2015 and March 19, 2016, 473 patients were screened for the study and 202 (43%) were found to be eligible and recruited in this trial. Of the eligible participants, 162 were randomly assigned into the treatment groups. Three patients in the medroxyprogesterone acetate group discontinued their therapy because of increased bleeding (two patients) and hysterectomy (one patient). Figure 1 displays the trial profile. For data analysis, the intention-to-treat approach was adopted. The dropout rate was less than 10%, and the missing values were replaced by the mean of the other group (17).

Almost all differences in patients' baseline characteristics following randomization were not significant except for the mean number of pregnancies and mean contraception duration (Table 1). Objectively measured menstrual blood loss assessed by the PBAC score was significantly reduced in both the cupping group and medroxyprogesterone acetate group compared to baseline measurement in both one and three month after the intervention. At one and three months, PBAC scores were significantly lower in women treated with cupping compared to women treated with medroxyprogesterone acetate; these reductions in PBAC score were 214.9 mL, with 95% CI (120.5 to 309.2), and greater than medroxyprogesterone acetate at 1 month and 237.3, with 95% CI (143.0 to 331.7) at 3- month follow- up (Table 2). A similar trend was found in PBAC percentage change at 1 and 3- month follow up, with respect to baseline in both intervention groups, which was significantly reduced (Table 2). Also, the percentage reduction was 28.4%, with 95% CI (17.5% to 39.3%) greater than the medroxyprogesterone acetate group at 1 month, and 35.8%, with 95% CI (24.9% to 46.6%) at 3- moth follow- up, which was significantly different between the 2 groups (Table 2).

Subjectively measured menstrual symptoms of number of bleeding days were reported at baseline, 1, and 3-

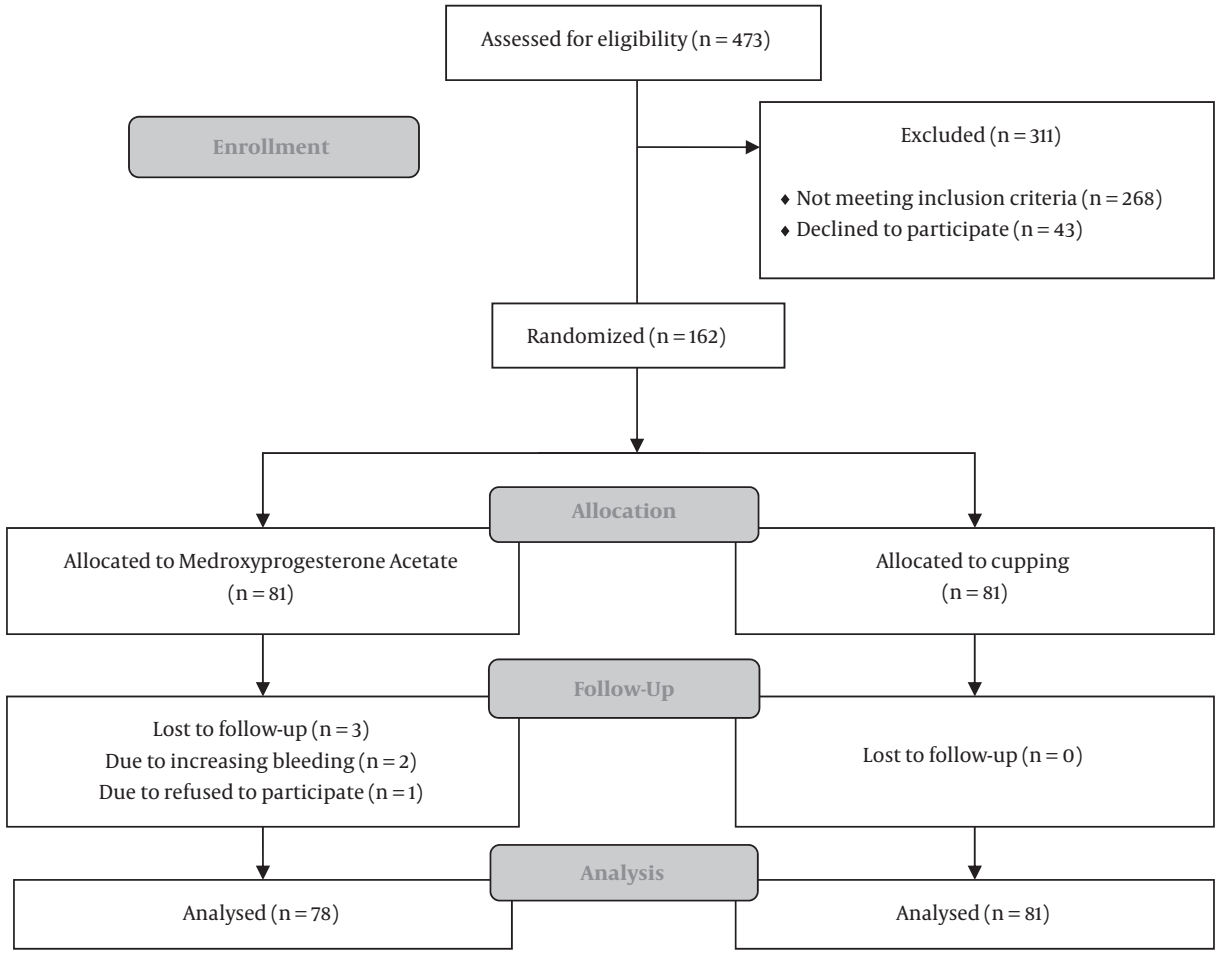

Figure 1. Flowchart of Participants Recruitment

month of follow- up separately for each treatment group (Table 3). The reduction of number of bleeding days was not significant. Also, adjusted changes from baseline on number of bleeding days between the 2 groups were not significant at both months. However, unadjusted comparison revealed a significant difference between the 2 groups. In other words, a reduction in the number of bleeding days in the cupping group, almost one day, was better than the control groups at one and three months follow- up (Table 3). The overall trend on number of bleeding days at baseline, 1 and 3-months follow up was incomparable to PBAC reduction over time and PBAC differences between the study groups in each time although all were not generally significant.

4. Discussion

The findings of the present study revealed that mean volume of bleeding one and three months after the trial, the number of days of menstruation, and the number of used pads were significantly reduced in the cupping group compared to the control group (those that took medroxyprogesterone acetate). Although few studies have been conducted on the use of medicinal plants to reduce menstrual bleeding (18, 19), there was only one study on the effectiveness of dry cupping as before and after the intervention, with a limited sample size (n = 15) in India. In that study, a significant difference was found between the severity of the bleeding before and after the intervention (20). The results of the present study, because of the study design and larger sample size, confirmed the findings of Sultana study. In the before and after studies, considering the lack of parallel control group and random allocation pro-

Table 1. Comparison of Baseline Characteristics of the Participants[a]

Characteristics	Cupping, (N = 81)	Medroxyprogesterone Acetate, (N = 78)	P Value[b]
Age (y)	38.3 ± (9.01)	39.4 ± (7.05)	0.232
Marriage duration (y), Mean (± SD)	19.1 ± (8.53)	20.6 ±(8.15)	0.275
Marital status, N.(%)			0.065
Married	62 (77.5)	70 (89.7)	
Single	16 (20.0)	5 (6.4)	
Divorced	2 (2.5)	2 (2.6)	
Widow	0 (0.0)	1 (1.3)	
Gravidity, (range)	1.8 (0 to 5)	2.3 (0 to 10)	0.036
Duration of contraception, Mean (± SD)	8.8 ± (7.52)	2.98 ± (5.71)	< 0.001
Methods of contraception, N.(%)			0.648
Natural	45 (55.6)	36 (46.2)	
Condom	12 (14.8)	10 (12.8)	
Oral contraceptive	1 (1.2)	1 (1.3)	
Vasectomy	5 (6.2)	9 (11.5)	
Tubectomy	8 (9.9)	7 (9.0)	
Other	10 (12.3)	15 (19.2)	
Menstrual duration (Day), Mean (± SD)	14.6 ± (15.71)	12.2 ± (13.63)	0.291
Menstrual pain, N.(%)	53 (65.4)	52 (66.7)	0.789
History of abdominal surgery, N.(%)	42 (51.8)	37 (47.4)	0.632
History of hormone therapy, N.(%)	37 (45.7)	40 (51.3)	0.436

[a]Values given as mean ± SD (standard deviation), or No. (%) unless otherwise indicated.
[b]Student's t-test, Chi-Square test, P < 0.05 was considered significant.

cess, the results are influenced by two main bias sources (regression to the mean and the effect of baseline values) (21, 22). Therefore, such results are less reliable and valid. However, the present study with larger sample size (less random error), a parallel control group, and random allocation process confirmed the findings of Sultana study. The effect size of cupping in the study was significant, similar to that of other studies, and the severity of bleeding was reduced by about 350 units. In the present study, the mean reduction of bleeding in the cupping group during 2 months was estimated approximately as 357 units, which represents a considerable effect of this intervention. Although the effect of cupping on menstrual bleeding was examined only in the mentioned study and the present research, the impact of this intervention on a variety of outcomes (such as pain, hypertension, and rehabilitation of limbs) has been evaluated in several studies, of which the majority have confirmed the effectiveness of cupping (7, 8, 23). In gynecological studies, the effect of cupping on pain following delivery and dysmenorrhea has been approved (11).

Cupping was done as either dry cupping or wet cupping. Dry cupping is carried with a vacuum by pulling blood to the skin surface. The vacuum can be done in different ways (24). Several systematic reviews have been conducted to evaluate the effect of cupping on pain treatment (23, 25). The effectiveness of the mechanism of cupping is done through the manipulation of small myelinated peripheral nerve fibers in the muscle along with suction. By creating suction, signals are sent from the spinal cord to the midbrain and pituitary, and this leads to the release of substances such as enkephalin, dinorphine, and serotonin into the bloodstream and cerebrospinal fluid, which finally relieves the pain (26, 27). Several mechanisms are suggested for reducing the intensity of menstrual bleeding by cupping. One of the mechanisms is changes in endometrial vascular homeostasis by cupping (28, 29). Homeostasis or physiological cessation of bleeding is a reaction for stopping bleeding from cuts and injured vessels. In addition, regulatory, restrictive, and digestive nature of blood clots should also be considered as components of the homeostatic system (30). Cupping modifies the endometrial vascular homeostasis by suppressing vascular dilators (prostaglandin), increasing the level of platelet aggregation, and metabolizing like thromboxane and DGF2α (vasoconstrictors) (31). Cupping can also divert blood vessels from the endometrium of the uterus to the internal organs to reduce hyperemia (20). In this process, the effect of vascular dilators, such as prostaglandin E2 and prostacyclin, ultimately decreases menstrual blood flow. Prostaglandin (PGE2 and PGF2α) is secreted from the endometrium by the performance of progesterone during ovulation. Maximum concentration is at the time of disposal of the endometrium layer. Previous studies have shown that the intensity of menstrual bleeding and menstrual pain has strong direct correlation with the amount of prostaglandins (32-36).

The study has some strengths that can be mentioned. Larger sample sizes reduced random error and increased reliability. The design study was a clinical trial, and then, randomization equally allocated confounding factors in all groups. Several outcomes were studied and led to bet-

Table 2. Pictorial Blood Loss Assessment Score[a]

Time/PBAC Score	Cupping, (N = 81)	Medroxyprogesterone Acetate, (N = 78)	Estimated Difference, (95% CI)[a]	P Value[b]
Mean of PBAC score, mL				
Baseline (SD)	546 (363.39)	557.3 (335.14)		
1 month (SD)	230.2 (144.29)	448.8 (245.20)	-215.7 (-283.5 to -147.9)[c]	< 0.0001
3 month (SD)	149.8 (124.19)	388.3 (333.87)	-237.3 (-305.1 to -169.5)[c]	< 0.0001
Change from baseline in PBAC Score, mL				
1 month			-214.9 (-309.2 to -120.5)	< 0.0001
Mean (SD)	-326.3 (318.0)	-110.7 (267.8)		
Median (range)	-232.5 (-1173 to +119)	-58 (-987 to + 884)		
3 month			-237.3 (-331.7 to -143.0)	< 0.0001
Mean (SD)	-410.0 (339.5)	-168.9 (276.0)		
Median (range)	-319 (-1340 to +7)	-115.5 (-1024 to +672)		
Percentage change from baseline in PBAC Score, mL				
1 month			-28.4 (-39.3 to -17.5)	< 0.0001
Mean (SD)	-46.2 (34.0)	-17.5 (35)		
Median (range)	-49.2 (-100.0 to +92.2)	-17.4 (-83.7 to 89.3)		
3 month			-35.8 (-46.6 to -24.9)	< 0.0001
Mean (SD)	-64.6 (26.2)	-27.7 (40.9)		
Median (range)	-69.3 (-100.0 to +13.2)	-24.6 (-100.0 to +107.6)		

Abbreviations: CI, Confidence Interval; PBAC, Pictorial Blood Loss Assessment Chart; SD, Standard Deviation.
[a] Estimated difference from statistical mixed model analysis.
[b] P value shown for planned analyses only, ANOVA test, P < 0.05 was considered significant.
[c] Adjusted on PBAC baseline measure.

ter decision- making for effectiveness of the intervention. One of the limitations of the study was the open-label design, which caused information bias, resulting in self-report outcomes. Based on the findings of the previous studies, PABC is associated with overestimation of bleeding (mean severity of bleeding) in the source population, and most likely, the study results corresponded with existing information.

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Table 3. No. of Bleeding Days in Treatment Groups[a]

Time/PBAC Score	Cupping, (N = 81)	Medroxyprogesterone Acetate, (N = 78)	Estimated Difference, (95% CI)[a]	P Value[b]
Mean of bleeding days				
Baseline (SD)	8.8 (3.4)	9.1 (2.9)		
One month (SD)	7.7 (1.2)	8.7 (3.4)	-0.94 (-1.68 to -0.20)[c]	0.013
Three month (SD)	7.3 (1.1)	8.3 (3.0)	-1.03 (-1.78 to -0.26)[c]	0.007
Change from baseline in No. of bleeding days				
One month			-0.76 (-1.89 to +0.37)	0.188
Mean (SD)	-1.14 (3.4)	-0.37 (3.6)		
Median (range)	0 (-21 to +3)	0 (-15 to +3)		
Three month			-0.80 (-1.93 to +0.33)	0.167
Mean (SD)	-1.57 (3.4)	-0.72 (3.9)		
Median (range)	-1 (-22 to 2)	0 (-15 to +3)		
Percentage change from baseline in bleeding days				
One month				
Mean (SD)	-7.6 (19.8)	-0.8 (36.1)	-6.7 (-15.9 to + 2.5)	0.151
Median (range)	0.0 (-75.0 to 42.8)	0.0 (-68.2 to + 60.0)		
Three month			-8.6 (-18.6 to +0.5)	0.065
Mean (SD)	-12.6 (18.8)	-3.3 (37.2)		
Median (range)	-12.5 (-78.5 to 25.0)	0.0 (-68.4 to +37.5)		

Abbreviations: CI, Confidence Interval; PBAC, Pictorial Blood Loss Assessment Chart; SD, Standard Deviation.
[a] Estimated difference from statistical mixed model analysis
[b] P-value shown for planned analyses only, calculated based on mixed model.
[c] Adjusted on PBAC baseline measure

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