Title page

The effect of caffeinated versus decaffeinated drinks on overactive bladder symptoms: a double-blind randomised cross-over pilot study.

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Key Words: Overactive Bladder, Caffeine

Abstract

Background

Evidence for the effects of caffeine on symptoms of overactive bladder (OAB) is limited; hence there is an urgent need for further trials. The primary aims of this pilot study were to test the methodology for use in a future randomised control trial and to investigate the effect of drinking caffeinated versus decaffeinated fluids on symptoms of OAB in women.

Methods

A double-blind, randomised, crossover study was conducted. Fourteen community-dwelling women newly diagnosed with OAB, with a history of caffeine consumption, were randomly allocated to Group A (14 day caffeinated drink period followed by 14 day decaffeinated drink period) or Group B (14 day decaffeinated drink period followed by 14 day caffeinated drink period). The periods were preceded by a 14-day run-in period and interspersed with a 14 day washout period. Primary outcomes were episodes of urgency, frequency, volume per void, and incontinence obtained each period using 3-day bladder diaries. Secondary outcome measures were OAB symptom severity and quality of life (QoL) measured each period using ICIQ-OAB and ICIQ-OABqol tools. Effects of caffeine reduction were measured each day using visual analogue scales.

Results

Eleven participants completed the study. A significant reduction in urgency ($p<0.01$) and frequency ($p<0.05$) of urinary voids on day 3 of the diary, total ICIQ-OAB score ($p<0.01$), and a directional change for the total ICIQ-OABqol score ($p=0.065$) was found using sign

tests for the period of decaffeinated compared to caffeinated drink intake. No significant differences were found for any caffeine withdrawal measures.

Conclusions

Despite the small sample size, this pilot study demonstrated that reducing caffeine intake may significantly alleviate the severity of some symptoms and QoL factors associated with OAB. Furthermore it may be concluded that caffeine substitutes were well tolerated.

Background

Overactive bladder (OAB) symptom based condition is defined as "urgency with or without urgency incontinence usually with frequency and nocturia in the absence of an underlying metabolic or pathological condition" (Abrams et al 2009). It is reported to be common, with prevalence in adult females varying from 7.7% to 31.3% (Abrams et al 2009). OAB and its management can have a significant impact upon health-related quality of life (QoL) (Bartoli et al 2010, Sexton et al 2011, Marinkovic et al 2012). OAB symptoms are burdensome and can affect emotional well-being and work productivity (Irwin et al 2006, Coyne et al 2008, Bartoli et al 2010).

The International Consultation on Incontinence (ICI) (Abrams et al 2009) recommends conservative treatment as first-line therapy for OAB. Conservative treatment includes lifestyle interventions, such as fluid and dietary intake modification (Abrams et al 2009). One such modification proposed is reduction in caffeine intake (Gungor and Beji 2011, Rai et al 2012).

Caffeine is a commonly ingested psychoactive substance, usually consumed within fluid in the form of coffee, tea and cola drinks (Heckman et al 2010, Penolazzia et al 2012). Other dietary sources include chocolate and energy drinks (Heckman et al 2012, Penolazzia et al 2012). The caffeine concentration in drinks varies, with coffee tending to have high levels compared to other drinks (Heckman et al 2010).

Once consumed, caffeine is rapidly absorbed and metabolised, exerting a variety of physiological actions (Heckman et al 2010). Regular caffeine consumers have been reported to exhibit symptoms of dependence (Striley et al 2011), and caffeine abstinence following

habitual consumption has been associated with symptoms such as fatigue, difficulty concentrating and headaches (Juliano et al 2012). Caffeine is known to cause a mild diuresis (Riesenhuber et al 2006; Lohsiriwat et al 2011) which may result in increased urinary frequency and may also affect detrusor stability (Creighton and Stanton 1990). Higher caffeine intakes have been associated with urinary incontinence (UI) (Gleason et al 2013) and caffeine intake has been associated with OAB.

NICE Guidelines (NICE, 2006) recommend a trial of caffeine reduction for the treatment of women with OAB; however, they also state that there is a lack of high-quality prospective controlled trials evaluating the effects of modifying lifestyle factors. There is a need for further evidence to provide clear evidence of benefit (or lack of it) of caffeine reduction on symptoms of OAB. The objectives of this pilot study were firstly to appraise methodology for a future larger scale study, and secondly to investigate the effect of drinking caffeinated versus decaffeinated fluids on symptoms of OAB in adult women.

Methodology

Trial design

A double-blind randomised cross-over study design was adopted (Figure 1). Following an initial 14 day run-in period, two 14 day intervention periods were separated by a 14 day washout period. Group A received caffeinated tea and coffee in period 1 and decaffeinated tea and coffee in period 2, whereas Group B received the same products in reverse order. Ethical and governance approvals were obtained from North and East Devon Research Ethics Committee (06/Q2102/41), Exeter, Mid Devon and East Devon Primary Care Trusts, and the Royal Devon and Exeter NHS Foundation Trust. Written informed consent was obtained from all participants.

Participants and study setting

Participants were recruited via nursing or medically run continence clinics in community and hospital settings in South West England and an advertisement in one edition of a local daily newspaper. Women over 18 years of age, newly diagnosed with OAB symptoms were invited to take part. Those who expressed an interest in taking part were informed verbally of the nature of the study and provided with a participant information sheet, 3-day bladder diary and consent form to return in the post if they agreed to participate. Women who met the inclusion and exclusion criteria were considered eligible for enrolment in to the study. Inclusion criteria were: women aged over 18 years; reported frequency of seven or more voids per day and two at night; self-rated urgency and/or UI; consumption of two or more caffeinated drinks per day (minimum caffeine content of 60 mgs per 24 hours). Exclusion criteria were: symptoms of stress incontinence only reported; oestrogen-containing oral contraceptive prescription; caffeine containing and caffeine metabolism interfering medication prescription; post-void residual greater than 100mls; history of frequent urinary tract infections; pregnancy; inability to complete a 3-day bladder diary; reported smoking habit. The Leicester Urinary Symptom Questionnaire (Shaw et al., 2002) was used to detect urinary tract symptoms.

Interventions

Participants were supplied with caffeinated and decaffeinated tea and coffee products for the duration of the trial by a commercial organisation. Products were considered identical in colour and taste and issued in beverage containers such as those normally available for purchase in supermarkets but with original labelling and packaging removed. During the run-in and washout periods participants were provided with tea and coffee labelled

'Decaffeinated'. During the intervention periods the tea and coffee products were labelled 'Product A' or 'Product B' and were either caffeinated or decaffeinated respectively.

Run-in period

At the start of the run-in period participants attended a one hour appointment with a researcher where the 3-day bladder diary supplied during recruitment was reviewed to confirm eligibility for the study. The International Consultation on Incontinence Modular Questionnaire - Overactive Bladder Module (ICIQ-OAB) and International Consultation of Incontinence Modular Questionnaire – Overactive Bladder - Quality of Life (ICIQ-OABqol) were also completed and demographic information recorded. 3-day bladder diaries (one for each period), Caffeine Withdrawal Visual Analogue Scales (CW-VAS) (one for each day of the trial) and a recording sheet for caffeine containing foods and instructions on how to complete them were provided. Equipment and instructions to provide daily saliva samples were also provided.

Decaffeinated tea and coffee products were issued for the run-in period and participants were asked to reduce their caffeine intake by replacing one cup of caffeinated tea or coffee with one cup of decaffeinated tea or coffee every day. Participants were asked not to drink caffeinated drinks other than those provided by the study and to record consumption of any caffeine containing products. A list of over-the-counter medications was provided and participants requested to avoid their purchase; if this was not possible they were asked to make a note of the type, quantity and date taken.

Intervention and wash-out periods

During period 1 Group A were supplied with caffeinated tea and coffee products and Group B with decaffeinated tea and coffee products (Figure 1). At cross-over Group A were supplied with decaffeinated fluids and Group B with caffeinated fluids for period 2 (Figure 1). Participants were instructed to consume an amount similar to their usual number of drinks and to refrain from drinking any caffeinated drinks. A 14 day washout period between periods 1 and 2 was conducted during which participants were asked to drink decaffeinated drinks only; however they were also given the option to replace caffeinated drinks one by one during these periods depending upon their ability to tolerate caffeine reduction, as per the run-in period.

Outcomes

A 3-day bladder diary (Dmochowski et al., 2005) was used to record fluid intake (size and type of drink), urine output (mls), time of voiding (to calculate frequency), urgency (1 to 5 scale) and incontinence over 3 days towards the end of the run-in, period 1, period 2 and the wash-out period. Secondary outcome measures included the ICIQ-OAB (Jackson et al., 1996, British Urological Institute Website 2012), ICIQ-OABqol (Coyne et al., 2003, British Urological Institute Website 2012) questionnaires, and CW-VAS (Rogers et al., 2005). The ICIQ-OAB evaluates symptoms and impact of overactive bladder and contains 4 items assessing frequency (how often do you pass urine during the day?), nocturia (during the night how many times do you have to get up to urinate on average), urgency (do you have to rush to the toilet to urinate) urge urinary incontinence (does urine leak before you can get to the toilet?). Bother associated with each item is also recorded on a 0 to 10 scale.

The ICIQ-OABqol contains 26 items and explores the impact on people's lives of overactive bladder. Respondents are asked to indicate how often bladder symptoms have impacted on

general activities on a 1 to 6 scale (none of the time to all of the time) for the first 25 items and a 0 to 10 scale (not at all to a great deal) for the final item. Participants were asked to complete the questionnaires based on their bladder activity in the previous 2 weeks towards the end of the run-in, period 1, period 2 and the wash-out period. 100 mm CW-VAS were completed every day throughout the trial to evaluate caffeine withdrawal symptoms. Characteristics measured on waking included ease sleep, restful sleep, often wake, ease waking, lively, muzzy, drowsy, headache and on retiring lively, tense, sad, muzzy, drowsy, attentive, sociable and headache.

Sample Size

As the study was a pilot no power calculations to determine sample size were undertaken. It was anticipated that the outcomes of this study will inform the numbers required for a full-scale trial.

Randomisation

Participants were randomly assigned following a simple randomisation procedure (random number generator) to Group A or Group B. The tea and coffee products provided for the intervention periods were labelled ‘Product A’ or ‘Product B’ and participants and investigators were not informed which products were caffeinated. The decaffeinated and caffeinated tea and coffee products were unbranded, designed to be identical in colour and taste and issued in typical beverage containers. The allocation sequence, enrolment and assignment of participants were carried out by one researcher.

Participant compliance was determined by the measurement of the caffeine content of saliva samples as compared to a measurement obtained at baseline. Measurement of caffeine in

saliva is a good measure of caffeine consumption as concentrations of caffeine in blood are proportional to caffeine levels in saliva (Biederbick et al., 1997; Newton et al., 1981). Participants were requested to collect daily saliva samples using a dental roll for the duration of the study. Samples were stored in the participant's refrigerator in a plastic container of double thickness with a secure press-down lid, labelled only with an ID number, and the date and time of sample collection. Participants were requested to post the samples to ABS Laboratories (South East London, UK) for caffeine assay analysis in a pre-addressed, strong padded envelope labelled with 'handle with care' at the end of each 14 day study period.

Statistical methods

Date were analysed by 2 way repeated measures analysis of variance (ANOVA) and Sign test using Stata (StataCorp LP) and SPSS version 17.0 for Windows (SPSS Inc., Chicago, Illinois, USA). An intention-to-treat analysis was applied such that all subjects who completed both arms of the study were included (whether they complied or not) in the analyses. Data from periods 1 and 2 are presented.

Results

Participant flow through the study from initial recruitment to completion is outlined in Figure 2. Of the 47 women that initially expressed interest, 16 (34%) consented to the study and 15 proceeded to take part. One participant dropped out following the run-in period due to intolerance to caffeine reduction. Three participants withdrew during the study due to health reasons not associated with the study itself, resulting in 11 participants following the study through to completion. This 21.4% drop-out rate is comparable to the 22% reported in a larger study looking at the effects of caffeine in conjunction with bladder training on OAB on 95 adults (Bryant et al. 2002).

Participants were recruited from July 2006 to October 2008. The trial was terminated when a sufficient number of participants were recruited to provide results for the pilot study and the funding period had terminated.

Baseline data

Eleven women (mean age 52 yrs.; range 27 yrs to 79 yrs.) were randomised into Group A (n=5) or Group B (n=6).

Numbers analysed

Data from the eleven participants who completed the study was included in the analysis.

Outcomes

3-day bladder diary

Table 1 shows the results of the 3-day bladder diary recordings. Sign test indicated a significant decrease in urgency episodes ($p<0.01$) and in frequency ($p<0.05$) on day 3 during the period of caffeine drinks vs. decaffeinated drinks. No other significant differences were detected using sign test between periods in the 3-day bladder diary on any day or overall.

ICIQ-OAB and ICIQ-OABqol

Table 1 shows some differences in recorded quality of life and symptoms between the decaffeinated and caffeinated drinks periods. ANOVA showed no significant effect of group ($F(1, 23) = 0.13$, $p>0.05$), period ($F(1, 23) = 2.04$, $p >0.05$) or interaction effect ($F(1, 23) = 1.49$, $p>0.05$) on ICIQ-OAB overall score. However, sign test indicated a significant

difference in the ICIQ-OAB overall score, with a greater value recorded during the periods of caffeine drinks compared to decaffeinated drinks ($p \leq 0.01$). A greater score is indicative of increased symptom severity. With regards to specific question items sign test indicated a significant decrease in nocturia ($p \leq 0.05$) and the number of episodes of urgency ($p \leq 0.05$) during the caffeine drinks treatment period; furthermore the latter symptom was significantly less bothersome when drinking decaffeinated drinks (median: 7 (IQR 4 to 8) compared with 4 (IQR1.5-6); $p=0.008$).

ANOVA showed no significant effect of group ($F(1, 23) = 1.18$, $p>0.05$), period ($F(1, 23) = 0.19$, $p >0.05$) or interaction effect ($F(1, 23) = 0.03$, $p>0.05$) on the ICIQ-OABqol overall score, although the median total score for the ICIQ-OABqol suggests a trend towards a better QoL during the period of decaffeinated drinks. Results from the ICIQ-OABqol (Table 1) show that significantly greater scores were recorded during the caffeinated drinks treatment period for item 9 (ability to get a good night's rest) ($p \leq 0.01$), item 13 (anxiety or worry) ($p \leq 0.05$), item 18 (awakened during sleep) and item 28 (interference with everyday life overall ($p \leq 0.01$).

CW-VAS

Sign test indicated no significant differences for symptoms of caffeine withdrawal measured by CW-VAS between the periods of caffeinated and decaffeinated drinks, indicating that the participants experienced similar symptom severity whether they were drinking caffeinated or decaffeinated drinks. Moreover this relationship is supported by subjective reports from the participants upon study completion. Seven of the women (63.6%) could not correctly identify during which period they were consuming caffeinated or decaffeinated drinks when

asked ‘do you think you were drinking fluids which contained caffeine in the first testing period or the second testing period and why?’

Compliance

The level of caffeine present in each participant’s saliva was determined from four random daily saliva samples for each treatment period and compared to a reference baseline level. A range from 0.1µg/ml to 30µg/ml was used to measure caffeine levels. Results suggested that 2 of the 11 participants that completed the study did not comply with caffeine substitution at the time points measured.

Discussion

Despite the small sample size, this study has indicated that reducing caffeine intake by replacing caffeinated with decaffeinated beverages may significantly alleviate OAB symptoms. These results support those found in a larger prospective randomised control trial (Bryant et al 2002), which reported a significant reduction of episodes of urgency and number of voids per 24 hrs in a group receiving bladder training and educational intervention to reduce caffeine intake. Notably in the study by Bryant et al (2002) participants were not blinded to group allocation which may have contributed towards the larger effect size than was found in our study. More recently the effect of caffeine ingestion (4.5 mg/kg) on bladder function in adults with OAB has been shown to promote urgency and frequency in a laboratory setting (Lohsiriwat et al 2011). Although the effect size obtained in this study was modest, it is similar to that reported in studies looking at the effects of anticholinergic agents for symptoms of OAB using similar outcome measures (Chapple et al 2008).

Although the existence of a caffeine withdrawal syndrome is well established, even in low to moderate users of caffeine (Juliano et al 2012), we did not find any of the caffeine withdrawal symptoms as measured on the VAS to be significant for the 11 participants that completed this study. This suggests that the caffeine substitutes were well tolerated in this study; an outcome which could be used to encourage recruitment in future studies where caffeine withdrawal is a main concern or reason for not participating. Compliance was objectively assessed in this study. Two participants appeared to have consumed caffeinated drinks during the decaffeinated drink period. However, only four random daily saliva samples for each treatment period were analysed so information on the compliance over the whole treatment period is absent. A future trial should consider the value of episodic analysis as a method of measuring compliance.

When considering study feasibility, one of the primary issues we encountered was participant recruitment. One of the main reasons for this was because potential participants opted to seek treatment rather than go through the trial first. For future trials we recommend that participants are recruited through multiple centres that offer first-line conservative treatment prior to commencing medication.

The crossover design adopted allowed for within-participant comparison between periods, with each person serving as his or her own control, thereby eliminating between-subject variability. The design appeared acceptable to the participants who completed the study and sensitive to the outcomes measured. The 14 day run-in period acted as a precaution to decrease symptoms of caffeine withdrawal prior to intervention and may have increased subsequent participant compliancy; therefore we recommend this for future trials. The quantity of paperwork associated with the participant orientated outcome measures used in

this trial was high, although it was generally reported to be quick and easy to complete by participants. In future trials we suggest that the use of the CW-VAS is reduced or removed to reduce participant load.

A drop-out rate of 21.4% was reached in our study. This could be attributed to the relative complexity of the study design and the length of the trial; it has been shown that by lengthening the amount of time a participant is on study, such as with a crossover design, the potential for participant loss and missing data is increased (Correa and Bellavance, 2001). However it is noted that the level is comparable to the 22% rate reported in a larger randomised control trial by Bryant et al (2002).

Recommendations for future studies include a randomised control trial. Although this would require a greater number of participants, it may reduce non-compliance and drop-out as it would provide a simpler parallel arm participant flow. The number of participant reported outcome measures used should be minimised to also reduce the complexity of the study; however the use of the 3-day bladder diary, ICIQ-OAB and ICIQ-OABqol is recommended to obtain data on clinical symptoms and QoL. An increase in the length of time participants' are exposed to an intervention should be considered in order to examine the longer-term effects of caffeine on OAB. If this were adopted we recommend outcome measure data to be collected at the beginning (baseline), middle and end of the trial.

Conclusion

This small cross-over study of caffeinated drink substitution indicates that the abstinence of caffeine may alleviate OAB symptoms. Although a modest effect size is likely, caffeine substitution is a relatively easy, low risk and painless intervention to implement and appears

to be well tolerated and interchangeable as a lifestyle intervention. It is recognised that future larger trials are needed to demonstrate these findings more robustly. The primary issues of recruitment, drop-out rate and non-compliance are likely to be important factors to consider in future trials.

Key points

- Replacing caffeinated drinks with decaffeinated drinks in the short term can improve symptoms of OAB
- Replacing caffeinated drinks with decaffeinated drinks is an acceptable, simple, lifestyle intervention
- A large trial should be conducted to evaluate the longer-term effect of reducing caffeine intake on symptoms of OAB

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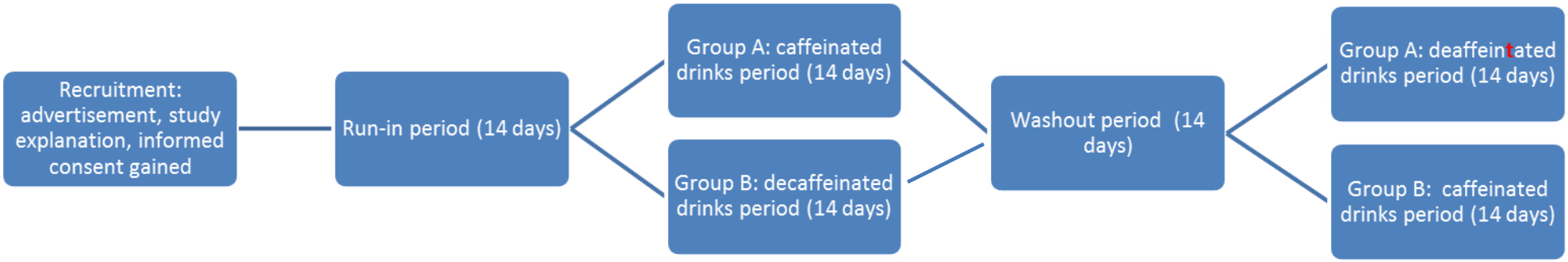

Figure 1: Study design showing study periods

Figure 1: Participant flow through study

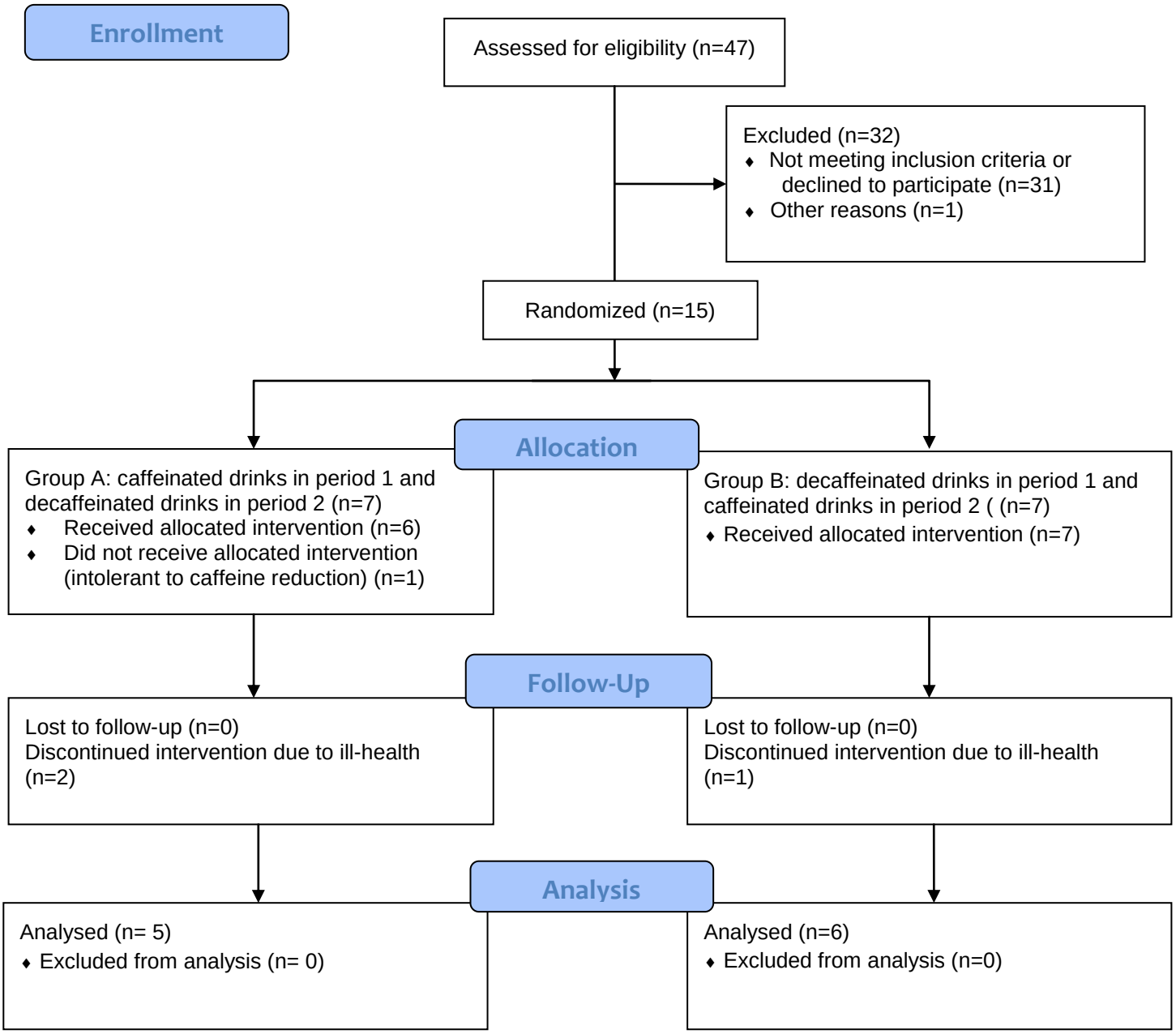

Table 1: Clinical symptoms and health-related quality of life characteristics for the caffeinated drink period and decaffeinated drink periods

Outcomes		Caffeine drink period: median (interquartile range)	Decaffeinated drink period: median (interquartile range)	Sign test significance value
3 day bladder diary items				
Urgency	d 1	9 (7.5-9.5)	7 (6-9)	ns (p=1.00)
(episodes/day)	d 2	9 (7.5-9.5)	7 (6-8.5)	ns (p=0.51)
	d 3	9 (7.5-10)	8 (6-8.5)	p=0.008
Overall		27 (22-28.5)	21 (18.5-25.5)	ns (p=0.73)
Frequency	d 1	9 (8-10)	7 (6-11)	ns (p=1.00)
(episodes/day)	d 2	9 (8.5-10)	7 (6.5-10)	ns (p=0.51)
	d 3	9 (7.5-11)	8 (7-10)	p=0.039
Overall		27 (22-31.5)	22 (19.5-31)	ns (p=1.00)
Volume	d 1	200 (174-237)	185 (152-229)	ns (p=0.55)
(mls per void)	d 2	220 (149-249)	193 (150-261)	ns (p=1.00)
	d 3	201 (173-257)	201 (147-279)	ns (p=1.00)
Overall		210 (172-247)	193 (154-255)	ns (p=1.00)
Incontinence	d 1	0 (0-1)	0 (0.5)	ns (p=0.69)
(episodes/day)	d 2	0 (0-1)	0 (0)	ns (p=0.63)
	d 3	0 (0-1)	0 (0-1)	ns (p=1.00)
Overall		1 (0-4)	0 (0-2.5)	ns (p=0.22)
ICIQ-OAB items				
Frequency (0 to 4)		1 (1-2)	0 (0-1)	ns (p=0.29)
Nocturia (0 to 4)		2 (1.5-2.5)	1 (1-2)	p=0.031
Urgency (0 to 4)		2 (1.5-2.5)	1 (1-2)	p=0.016
Urge Urinary Incontinence (0 to 4)		1 (1-1.5)	1 (0-1)	ns (p=0.38)
Overall bother (n=10) (0 to 40)		26 (15-32.5)	16 (12-22)	ns (p=0.1)
Overall score (0 to 16)		6 (5.5-9.0)	4 (3.5-5.5)	p=0.002
ICIQ-OABqol items				
3 Journey planning (1 to 6)		3 (2-4)	2 (1.5-3)	ns (p=0.45)
4 Tired (1 to 6)		3 (2-3.5)	2 (1-3)	ns (p=0.13)
5 Toilet access (1 to 6)		3 (2-4)	2 (1.5-3)	ns (p=0.18)
6 Distress (1 to 6)		3 (1.5-3)	2 (2-2)	ns (p=0.29)
7 Frustration (1 to 6)		3 (2.5-3)	2 (2-3)	ns (p=0.51)
8 Feel something wrong with self (1 to 6)		3 (2.5-4)	2 (1-3)	ns (p=0.07)
9 Inadequate sleep (1 to 6)		4 (3.5-5.5)	2 (2-3.5)	p=0.004
10 Physical activities (1 to 6)		1 (1-2.5)	1 (1-2)	ns (p=1.00)
11 Not rested on waking (1 to 6)		3 (2.5-4.5)	2 (1.5-3.5)	ns (p=0.22)
12 Frustration for family/friends (1 to 6)		1 (1)	1 (1)	ns (p=1.00)
13 Anxiety/worry (1 to 6)		3 (2-3)	2 (1-2)	0.016
14 Restriction to home (1 to 6)		1 (1-2)	1 (1)	ns (p=0.50)
15 Adjusting travel to toilet location (1 to 6)		2 (1-4)	1 (1-2.5)	ns (p=0.13)
16 Avoid activities away from toilet (1 to 6)		2 (1-3.5)	2 (1-2.5)	ns (p=0.69)
17 Frustration over time spent in toilet (1 to 6)		3 (2.5-4.5)	2 (2-3.5)	ns (p=0.29)
18 Awakened during sleep (1 to 6)		4 (3-5)	3 (2-3)	0.039
19 Odour/hygiene (1 to 6)		2 (1.5-4)	2 (1-3)	ns (p=0.38)
20 Uncomfortable travelling with others (1 to 6)		2 (1.5-3)	1 (1-2.5)	ns (p=0.13)
21 Relationships (1 to 6)		1 (1)	1 (1)	ns

22 Social activities (1 to 6)	1 (1)	1 (1)	ns (p=1.00)
23 Embarrassment (1 to 6)	1 (1-2)	2 (1-2)	ns (p=0.69)
24 Interfered with sleep (1 to 6)	3 (3-5.5)	3 (1.5-3)	ns (p=0.07)
25 Problems with partner/spouse (1 to 6)	1 (1)	1 (1)	ns (p=1.00)
26 Plan activities (1 to 6)	3 (2-4)	2 (1-2)	ns (p=0.51)
27 Toilet location (1 to 6)	4 (2.5-5.5)	3 (2-5)	ns (p=0.38)
28 Overall impact on everyday life (1 to 10)	6 (4-6.5)	4 (2.5-5)	p=0.002
Overall score (25 to 160)	69 (54-75.5)	50 (44.5-57)	ns (p=0.065)

ns = not significant
ICIQ-OAB: International Consultation of Incontinence Questionnaire-Overactive Bladder
ICIQ-OABqol: International Consultation of Incontinence Questionnaire Overactive Bladder