Original Investigation

Comparing perioperative vaginal misoprostol to intraoperative pericervical hemostatic tourniquet in reducing blood loss during abdominal myomectomy: a randomized controlled trial

Afolabi et al. Reducing blood loss at myomectomy

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Abstract

Objective: To compare the effectiveness of perioperative vaginal misoprostol to intraoperative pericervical hemostatic tourniquet in reducing blood loss during abdominal myomectomy.

Material and Methods: A randomized controlled trial involving women with uterine leiomyoma who underwent abdominal myomectomy at a tertiary facility in Nigeria. Participants were recruited after informed consent and randomized into Group I (single dose 400 µg vaginal misoprostol one-hour before surgery) and Group II (intraoperative pericervical hemostatic tourniquet). Eighty participants (40 in each group) were recruited. Uterine size was measured in centimeter above pubic symphysis while blood loss estimation involved direct volume measurement and gravimetric methods. The main outcome measures were intraoperative blood loss, blood transfusion and recourse to hysterectomy. Ethical approval and trial registration were obtained; the data was analyzed using the SPSS software version 21.0 and $p < 0.05$ was significant.

Results: Participants in group I had higher mean intraoperative blood loss (931.89 ± 602.13 ml vs. 848.40 ± 588.85 ml, $p = 0.532$), intra-operative blood transfusion rate (60% vs. 55%; $p = 0.651$) and mean unit of blood transfused (1.30 ± 1.20 vs. 1.20 ± 1.30 ; $p = 0.722$) compared to group II. The mean uterine size (19.50 ± 6.93 vs. 20.05 ± 6.98 ; $p = 0.725$) and number of fibroid nodules (11.25 ± 7.99 vs. 11.45 ± 8.22 ; $p = 0.912$) were comparable. The change in post-operative hematocrit were ($2.66 \pm 2.21\%$ vs. $3.24 \pm 2.85\%$, $p = 0.315$) and post-operation blood transfusion (2.5% vs. 5%; $p = 0.556$). There was no recourse to abdominal hysterectomy while side effect of misoprostol occurred in 5 (12.5%) of group I participants.

Conclusion: The effectiveness of perioperative vaginal misoprostol is comparable to intra-operative hemostatic pericervical tourniquet in reducing blood loss during abdominal myomectomy.

Keywords: Uterine leiomyoma; Misoprostol; Hemostatic tourniquet; Abdominal myomectomy; Hemostasis.

Introduction

Uterine leiomyoma is the commonest benign genital tract tumor in women of reproductive age (1) and the commonest reason for gynecological consultation in most Nigerian hospitals (2,3). It is commoner among Black women (4) with an incidence of 3.0% to 29.3% (2,5). It may be asymptomatic with incidental discovery during pelvic examination or ultrasonography for other indications. Symptomatic uterine fibroid can adversely affect the quality of life, especially in low resource countries where patients often present late with huge masses and anemia (2,3,5). The definitive treatment for symptomatic leiomyoma is hysterectomy; however, for women desirous of future fertility or preservation of the uterus, myomectomy is a common option (6). Abdominal myomectomy is often preferred to laparoscopic route in the presence of large and multiple uterine leiomyoma (7).

Intraoperative hemorrhage necessitating blood transfusion is the commonest complication of abdominal myomectomy (4) and when uncontrollable, it may necessitate hysterectomy (8). The volume of blood loss at abdominal myomectomy depends on the uterine size, number and location of the leiomyoma (7). Generally, blood

transfusion rate for abdominal myomectomy is 13.5 to 58.2% (4,9) with 2% inadvertent hysterectomy rate following uncontrollable hemorrhage (6,9). Therefore, effective interventions to reduce blood loss remain desirable during myomectomy (10).

Methods of reducing hemorrhage during myomectomy include peri-operative vaginal misoprostol, intra-operative-myometrial vasopressin, intra-myometrial bupivacaine with epinephrine, intravenous tranexamic acid, gelatin-thrombin matrix, intravenous ascorbic acid, vaginal dinoprostone, loop ligation of the leiomyoma pseudo-capsule, fibrin sealant patch and per cervical tourniquet using Foley catheter (3). However, each method has its limitations; therefore, controlling hemorrhage remains a major task for gynecologists (11).

The Foley catheter, often improvised as tourniquet in low resource countries is cheap and readily available (12) but, requires intermittent release intra operation to prevent build-up of toxins, tissue ischemia and may be impracticable to apply sometimes (11). Once the tourniquet is removed, there is bleeding from the raw myometrium and cavities with possibility of increased blood loss and blood transfusion (13).

Misoprostol in addition to its role in managing miscarriages, pre-induction cervical ripening, and induction of labor, prevention and treatment of primary postpartum hemorrhage (14) has gained relevance in myomectomy. It increases myometrial contractions thereby reducing uterine artery blood flow (15) to the uterus. Its heat stability and long shelf life improves its availability in the tropics where huge leiomyoma are predominant while the multiple routes of administration increases choices and acceptability (16). The peak plasma level of 400µg of vaginal misoprostol is reached one to two hours after administration and is sustained till four hours (16) while the side effects are self-limiting (15,16). Reports on misoprostol use to control blood loss at abdominal myomectomy showed reduction in intra and post-operative blood loss, operation time and post-operative blood transfusion (6,15) but these were from developed countries. In practice, there are instances when application of the tourniquet is impracticable and another method is indicated. Therefore, this study was aimed to evaluate the effectiveness of vaginal misoprostol compared to hemostatic tourniquet in reducing hemorrhage at abdominal myomectomy.

Materials and Methods

Study Design

The study was a randomized controlled study conducted between June 2016 and May 2017 at the University of Ilorin Teaching Hospital- a tertiary health facility in North-central Nigeria with facilities for undergraduate and postgraduate medical training. The obstetrics and gynaecology department has 170 beds, an average annual delivery rate of 2000 and 500 gynecological admissions. Participants were women with symptomatic uterine leiomyoma who underwent abdominal myomectomy. The study evaluated the effectiveness of perioperative misoprostol administered vaginally compared with intraoperative pericervical hemostatic tourniquet in reducing blood loss during abdominal myomectomy. The inclusion criteria were a diagnosis of uterine leiomyoma and a decision for abdominal myomectomy. Women who had other forms of myomectomy, allergy to prostaglandins, chronic medical disorders, previous uterine surgery (myomectomy, caesarean delivery) and anemia (Hematocrit <10g/dl at 24 hour pre operation) were excluded from the study. The primary outcome measures were estimated intraoperative blood loss and the need for intraoperative blood transfusion. The secondary outcome measures were intraoperative recourse to hysterectomy, post-operative hematocrit change and side effects of misoprostol among Group I participants.

Sample size determination:

The sample size was calculated using a previously validated formula (17), the power set at 95%, the standard normal deviate corresponding to 5% level of significance and the mean intraoperative blood loss for hemostatic tourniquet (18) and misoprostol (15) of 286.4 ± 137.5 ml and 200.16 ± 18.8 ml from previous studies with 10% attrition rate to yield a sample size of 40 participants for each group and a total 80 participants.

Study protocol

All women with symptomatic uterine leiomyoma were informed about the study; interested individuals were then screened using the eligibility criteria followed by a written informed consent from eligible women. Consenting participants were randomized into either of two groups to receive perioperative vaginal misoprostol (Group I) or intraoperative pericervical hemostatic tourniquet (Group II). To allow randomization, researchers prepared the management protocol for each of the two groups and sealed one protocol per envelope with a computer generated number assigned. Randomization was by picking the numbered study envelopes sequentially and managing the participant based on the enclosed protocol. Participants were identified with the randomization number until discharge from the hospital. All participants had standard preoperative evaluation to include complete blood count, urinalysis, serum electrolyte, urea and creatinine, pelvic ultrasound scan for size, number and location of the

leiomyoma and hysterosalpingography. Other investigations were performed as indicated. Group I participants received two tablets of 200 μ g i.e. total of 400 μ g misoprostol (Pfizer Limited, United Kingdom) administered into the posterior fornix of the vagina at least one hour before the onset of the surgery. Group II participants had pericervical tourniquet using a Foley catheter size 18, tied firmly at the level of the cervico-isthmic junction of the uterus before the uterine incision. The time of administration of tourniquet was recorded and tourniquet was released not exceeding 45 minutes from its application. For those requiring multiple application, tourniquet was reapplied at least after a period of 15 minutes. All the procedures were performed in equal proportion by four consultant gynecologists of similar skill and experience while estimation of blood loss was by measurement of volume of blood in the suction bottle while other losses were accounted for using gravimetric method by mopping with pre-weighed abdominal mops and repeat measurement with one gram weight difference equivalent to 1ml of blood (19). The maximum allowable blood loss (transfusion trigger) was calculated for each participant and intraoperative blood transfusion was commenced when this was exceeded (20). Blood transfusion was also commenced with cardiovascular instability from hemorrhage or signs of inadequate perfusion or oxygenation. All participants were monitored until hospital discharge. Participants in group I were evaluated for side effects of misoprostol (nausea, vomiting, diarrhea, elevated temperature [$>38^{\circ}\text{C}$], shivering) within one hour and 24 hour post-surgery. All participants had hematocrit estimation at 24 hours post-surgery in addition to other routine post operation care.

Ethical Issue

Ethical approval was obtained from the ethical review committee of the University of Ilorin Teaching Hospital, Ilorin, Nigeria (ERCPAN/2015/09/1455; 10/09/2015) before commencement of the study. The trial was registered with the Pan African Clinical Trial Registry (www.pactr.org) with registration number PACTR201802003039106 while a written informed consent was obtained from all participants in the study.

Statistical analysis

The data obtained from this study were analyzed using Statistical Package for Social Sciences software (SPSS) version 21.0. Chi-square, T-test and Mann Whitney U test were used to describe variables as appropriate while $p < 0.05$ was considered significant.

Conflict of interest

The authors declare no conflict of interest in the conduct of the study; there was no financial relationship or sponsorship. The authors have full control of all the data which can be verified if required.

Results

A total of 120 women were screened for eligibility in the study but 80 (66.7% of total screened) participants comprising 40 in each of the two groups participated in the study. Figure 1 shows the flow chart for the trial. The age range of participants was 24 to 45 years (mean 36.4 ± 5.97), 47 (58.8%) were nulliparous while 51 (63.8%) had no child. The common presenting symptoms were excessive/prolonged menstrual flow (50; 62.5%), abdominal swelling (46; 57.5%) and inability to conceive (43; 53.75%) while 75 (93.7%) had multiple symptoms (table 1). There were similarities in the two groups relative to mean uterine size (19.50 ± 6.93 vs. 20.05 ± 6.98 ; $p = 0.725$) and mean number of fibroid nodules (11.25 ± 7.99 vs. 11.45 ± 8.22 ; $p = 0.912$) as shown in table 2. Intraoperative, group I participants recorded higher values in mean intraoperative blood loss ($931.89 \pm 602.13\text{ml}$ vs. $848.40 \pm 588.85\text{ml}$; $p = 0.532$), blood transfusion (24[60.0%] vs. 22[55.0%], $p = 0.651$) and mean number of units of blood transfused (1.30 ± 1.20 vs. 1.20 ± 1.30 , $p = 0.655$) than group II. Postoperative, blood transfusion was in 1(2.5) vs. 2(5.0%) in groups I and II as shown in table 3. The mean preoperative hematocrit were $33.78 \pm 2.70\%$ vs. $34.56 \pm 0.53\%$ ($p = 0.253$), mean post-operative hematocrit ($31.11 \pm 3.25\%$ vs. 31.32 ± 3.36 , $p = 0.782$) and mean hematocrit change ($2.66 \pm 2.21\%$ vs. $3.24 \pm 2.85\%$; $p = 0.315$) for groups I and II. Among the 34 participants (group I [16] and group II [18]) who did not receive intraoperative blood transfusion, the hematocrit change was similar ranging from 2 to 10.5% but these were not statistically significant as shown in table 4. From table 5, side effects of misoprostol occurred in 5 (12.5%) of group I participants while 2 (40.0%) experienced multiple side effects.

Discussion

In this study, the mean intra-operative blood loss, rate of intra-operative blood transfusion and number of units of blood transfused were higher among participants who had perioperative vaginal misoprostol compared to those who had intra-operative pericervical hemostatic tourniquet although these were not statistically significant. However, the change in post-operative hematocrit and rate of post-operation blood transfusion were higher in women who had intra-operative pericervical hemostatic tourniquet although not statistically significant. None of the participants in the study had recourse to hysterectomy while the side effects of misoprostol were minimal and self-limiting among women managed with misoprostol.

The strength of the study is that it compared perioperative misoprostol with hemostatic tourniquet which is uncommon in the literature, the randomized design and objective measurement of the blood loss. The limitations included the small sample size and the limited study area.

Misoprostol has been reported to be effective in reducing blood loss at myomectomy following comparison to placebo (21,22,23) or other agents (24). The mean blood loss following misoprostol administration in this study was higher than reports from Egypt (574 ± 194.8 ml) (23), Iran (458 ± 287 ml) (22) and Turkey (472 ± 77 ml) (21). A review of the methodology showed that these studies with lower blood loss had lower mean uterine sizes of (< 24 weeks) (23), (8.7 ± 4.6 weeks) (22) and (15.7 ± 2.6 weeks) (21) compared to 19.50 ± 6.93 in this study. This may explain the higher blood loss in this study as blood loss at myomectomy has been shown to be proportional to the uterine size. In addition, the number of fibroid nodules is related to the blood loss which explains the lower blood loss in the Turkish study with mean number of leiomyoma of 5.5 ± 1 leiomyoma (21) compared to 11.25 ± 7.99 in this study. Blood loss estimation remains central during abdominal myomectomy. In the Turkish (21) and Iranian (22) studies, the recorded blood loss was measured from the blood in the suction bottle while this study assessed other losses not in the suction bottle using gravimetric method.

Different studies used different dosing regimen for misoprostol in myomectomy. A study from Iran used $200 \mu\text{g}$ of vaginally administered misoprostol three hours prior to surgery (22) compared to $400 \mu\text{g}$ of vaginal misoprostol administered one hour prior to surgery in this study. This raises a future research question on the effect of dose and time interval from administration of misoprostol to commencement of surgery on the blood loss. Another study evaluated the effect of multiple dosing and reported higher blood loss (200.16 ± 18.8 ml vs. 101.4 ± 25.5 ml) (15) for single compared to two doses but higher side effects of misoprostol with multiple dosing. The concern of researchers remains the possible additive side effects of misoprostol with multiple dosing (15) which necessitated single dosing in this study. However, further comparison was limited by the smaller mean uterine size and number of leiomyoma (15.33 ± 8.48 weeks and 2.91 ± 4.24 leiomyoma) (15) compared to this study.

The intra-operation blood transfusion rate of 60% in this study was higher than previous reports of 15.3% (21) and 24% (23) while there was no blood transfusion in other reports (15,22). This may be attributed to the bigger uterine sizes, presence of multiple uterine fibroids and higher mean blood loss in this study. There is no consensus on the time to initiate blood transfusion during myomectomy. In this study, intraoperative blood transfusion was commenced when the calculated maximum allowed blood loss for the patient was reached or evidence of cardiovascular instability from hemorrhage. However, another study employed a loss of 2000 ml as indication for blood transfusion among the participants (22).

In this study, the mean pre-operative, post-operative and changes in hematocrit were not statistically significant. This emphasizes the comparative effectiveness in reducing blood loss by the two methods compared. In most of the studies comparing misoprostol to placebo, the misoprostol group had post-operative hemoglobin values that were significantly higher than those found in the placebo group (21,22,23). This validated the effectiveness and superiority of misoprostol which is an active agent over placebo in such studies.

The side effects of misoprostol experienced by participants in this study compares to previous reports; they were self-limiting and included nausea, vomiting, diarrhea, shivering and fever (15, 21,22,23). They either require no intervention or simple interventions to alleviate symptoms such as covering the patient with blankets for shivering. Other researchers have compared misoprostol with other agents in reducing blood loss at myomectomy. A comparison of effectiveness of the administration of a single preoperative dose of vaginal misoprostol with intraoperative oxytocin infusion on blood loss during abdominal myomectomy reported statistically significantly lower blood loss (401 ± 48 ml vs. 589 ± 49 ml) in the misoprostol group (24). Also, comparison of rectal misoprostol plus perivascular vasopressin with perivascular vasopressin alone reported statistically significantly lower blood loss (334 ml vs. 623 ml) in the former group (25). This implies that misoprostol compares favorably with other agents depending on the locally available alternatives in a number of settings.

The estimated blood loss from the tourniquet group in this study was higher than that 515.7 ± 292.81 ml reported by Ikechebelu in Nnewi, Nigeria (11). A possible explanation is the difference in blood loss estimation in the studies. Comparison of tourniquet to no-tourniquet use recorded significant reduction in blood loss in the tourniquet group (11, 18), while tourniquet use produced higher blood loss when compared to other hemostatic techniques like vasopressin or preliminary uterine artery ligation (25,26). However, there is paucity of data on comparing tourniquet with misoprostol in reducing blood loss during abdominal myomectomy.

In summary, this study suggests comparable effectiveness in reducing blood loss at abdominal myomectomy for peri-operative vaginal misoprostol and intra-operative hemostatic peri-cervical tourniquet. This is recommended for routine use especially in instances where application of the tourniquet is impracticable due to significant pelvic adhesions and leiomyoma in the broad ligament, uterine isthmus or cervix.

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Figure 1: Flow chat of participants in the trial

Table 1: Socio demographic characteristics of the study population

Variables	Freq (%) N=80
Age Groups(years)	
≤ 25	2 (2.5)
26 – 30	14 (17.5)
31 – 35	17 (21.2)
36 – 40	30 (37.6)
≥ 41	17 (21.2)
Mean ± SD	36.4±5.97
Marital Status	
Single	8 (10.0)
Married	71 (88.8)
Divorced	1 (1.2)
Educational Status	
None	6 (7.5)
Primary	13 (16.2)
Secondary	21 (26.3)
Tertiary	40 (50.0)
Parity	
0	47 (58.8)
1	20 (25.0)
2 – 4	12 (15.0)
≥ 5	1 (1.2)
Number of children alive	
0	51 (63.8)
1	17 (21.2)
2 – 4	11 (13.8)
≥ 5	1 (1.2)
Presenting symptom	
Irregular vaginal bleeding	2 (2.5)
Dysmenorrhea	12 (15.0)
Recurrent pregnancy losses	19 (23.8)
Recurrent abdominal pain	22 (27.5)
Inability to conceive	43 (53.8)
Abdominal swelling	46(57.5)
Excessive/prolonged menstruation	50 (62.5)
Single symptom	5 (6.3)
Multiple symptoms	75 (93.7)

Table 2: Intra-operative events of participants in the two groups

Variable	Group I N=40 (%)	Group II N=40 (%)	χ^2 /M-W U	p-value
Uterine size(wks)				
8-12	8 (20.0)	5 (12.5)		
14-18	13 (32.5)	16 (40.0)		
20-24	9 (22.5)	7 (17.5)		
26-30	9 (22.5)	9 (22.5)		
32	1 (2.5)	3 (7.5)	2.253	0.689
Mean $\pm$ SD	19.50 $\pm$ 6.93	20.05 $\pm$ 6.98	-0.353^T	0.725
Anaesthesia				
Regional	22 (55.0)	22 (55.0)		
Spinal	6 (15.0)	6 (15.0)		
Epidural	8 (20.0)	8 (20.0)		
Combined Spinal-Epidural	8 (20.0)	8 (20.0)		
General anaesthesia	18 (45.0)	18 (45.0)	0.000	1.000
Skin incision				
Pfannenstiel	20 (50.0)	21 (52.5)		
Midline infra-umbilical	9 (22.5)	7 (17.5)		
Midline infra-umbilical with supra-umbilical extension	11 (27.5)	12 (30.0)	0.318	0.853
*Location of fibroids				
Sub-serous	35 (87.5)	33 (82.5)	0.392	0.754
Intramural	39 (97.5)	39 (97.5)	0.513	0.474
Submucosa	20 (50.0)	21 (52.5)	0.05	0.823
Number of fibroid				
Sub-serous	1.67 $\pm$ 2.08	2.67 $\pm$ 2.42	0.000	1.000
Intramural	7.47 $\pm$ 6.34	7.73 $\pm$ 6.80	-0.170	0.865
Submucosa	0.90 $\pm$ 1.15	0.93 $\pm$ 1.31	-0.910	0.928
Mean $\pm$ SD	11.25 $\pm$ 7.99	11.45 $\pm$ 8.22	-0.110^T	0.912
Duration of surgery (minutes)				
< 60	52.00 $\pm$ 4.24	51.40 $\pm$ 5.89	0.128	0.903
60– 120	92.75 $\pm$ 18.93	92.32 $\pm$ 19.75	0.078	0.938
> 120	146.36 $\pm$ 23.01	152 $\pm$ 31.54	-0.508	0.617
Mean $\pm$ SD	109.48 $\pm$ 34.90	102.13 $\pm$ 38.76	0.891^T	0.376

M-W U: Mann Whitney-U test. χ^2 : Chi-square test. T: Independent standard t-test.

SD: Standard Deviation

*Some participants had fibroid masses in multiple locations

Table 3: Pre- operative, Intra-operative and post-operative intravenous fluid and blood transfusion management

Variable	Group I N=40 (%)	Group II N=40 (%)	χ^2 / T	p-value
Estimated blood loss(ml)				
< 500	11 (27.5)	12 (30.0)		
500 – <1000	16 (40.0)	18 (45.0)		
1000 – <1500	9 (22.5)	5 (12.5)		
1500 - < 2000	1 (2.5)	2 (5.0)		
>2000	3 (7.5)	3 (7.5)	1.637	0.802
Mean $\pm$ SD	931.89 $\pm$ 602.13	848.40 $\pm$ 588.85	0.627^T	0.532
Blood transfusion				

No	16 (40.0)	18 (45.0)		
Yes	24 (60.0)	22 (55.0)	0.205	0.651
Number of units				
0	16 (40.0)	18 (45.0)		
1	2 (5.0)	5 (12.5)		
2	18 (45.0)	11 (27.5)		
3	2 (5.0)	3 (7.5)		
4	2 (5.0)	3 (7.5)	4.383	0.223
Mean $\pm$ SD	1.30 $\pm$ 1.20	1.20 $\pm$ 1.30	0.358 ^T	0.722
Post-operation blood transfusion				
No	39 (97.5)	38 (95.0)		
Yes	1 (2.5)	2 (5.0)	0.346	0.556
Number of units				
0	39 (97.5)	38 (95.0)		
1	1 (2.5)	2 (5.0)		
Mean $\pm$ SD	0.05 $\pm$ 0.22	0.03 $\pm$ 0.16	0.582 ^T	0.562

χ^2 : Chi-square test. T=Independent Samples T test; SD: Standard Deviation

Table 4: Comparison of levels and changes in hematocrit among participants

Hematocrit (%)	Group I N=40 (%)	Group II N=40 (%)	χ^2/ M-WU	p value
Pre-Operation				
≥ 30 -33	20 (50.0)	18 (45.0)		
>33-36	14 (35.0)	11 (27.5)		
>36-39	5 (12.5)	6 (15.0)		
>39	1 (2.5)	5 (12.5)	3.223	0.359
Mean $\pm$ SD	33.78 $\pm$ 2.70	34.56 $\pm$ 0.53	-1.153 ^T	0.253
Post-operation				
≤ 30	16 (40.0)	20 (50.0)		
>30-33	15 (37.5)	12 (30.0)		
>33-36	9 (22.5)	6 (15.0)		
>36-39	0 (0.0)	1 (2.5)		
>39	0 (0.0)	1 (2.5)	3.378	0.497
Mean $\pm$ SD	31.11 $\pm$ 3.25	31.32 $\pm$ 3.36	-0.277 ^T	0.782
Mean Hematocrit change	2.66 $\pm$ 2.21	3.24 $\pm$ 2.85	-1.012	0.315
Hematocrit change among participants who were not transfused	n=16	n=18		
% change				
≤ 3	6 (37.5)	4 (22.2)		
4-6	1 (6.3)	2 (11.1)		
7-9	6 (37.5)	5 (27.8)		
>9	3 (16.7)	7 (38.9)	2.382	0.666

χ^2 : Chi-square test , M-W U: Mann Whitney U Test, T: Independent standard t-test.
SD: Standard Deviation

Table 5: Side effect profile of misoprostol among group I participants*

Variable	Frequency N=40 (%)
Nausea	
Yes	3 (7.5)
No	37 (92.5)
Vomiting	
Yes	1 (2.5)
No	39 (97.5)
Shivering	
Yes	3 (7.5)
No	37 (92.5)

*Some participants experienced more than one side effect

#There were no cases of diarrhea or pyrexia among participants