Oral Medroxyprogesterone Acetate and Combination Oral Contraceptives for Acute Uterine Bleeding

A Randomized Controlled Trial

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OBJECTIVE: To compare the efficacy of multidose medroxyprogesterone acetate and a multidose monophasic combined oral contraceptive (OC) for hemodynamically stable women with nongestational, acute uterine bleeding.

METHODS: Hemodynamically stable patients with acute uterine bleeding sufficient to justify immediate medical or surgical intervention were enrolled in an open-label, randomized trial comparing oral medroxyprogesterone acetate 20 mg and a monophasic combination OC containing 1 mg norethindrone and 35 μg of ethinyl estradiol, each administered three times per day. Doses were reduced after 1 week to 20 mg per day and one tablet per day for the next 3 weeks for the medroxyprogesterone acetate and OC groups, respectively. Following baseline assessment, patients completed daily treatment and symptom logs collected at 14 and 28 days after initiation of therapy.

RESULTS: Forty patients were randomly assigned, 20 in each group; 33 were evaluated at the 14-day visit. Emergency surgical procedures were avoided in 100% of those women taking medroxyprogesterone acetate and 95% of the OC group. Cessation of bleeding had occurred in 88% of the OC group and 76% of those receiving medroxyprogesterone acetate, with a median time to bleeding cessation of 3 days for both groups. Compliance with therapy was higher in the medroxyprogesterone acetate group than the OC group, but there was no overall difference in the incidence of treatment-related nausea and bloating.

CONCLUSION: This randomized trial is limited by sample size but suggests that both regimens may be effective and reasonably well tolerated.

CLINICAL TRIAL REGISTRATION: Current Clinical Trials (clinicaltrials.gov, www.clinicaltrials.gov) Identifier: NCT00350480

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LEVEL OF EVIDENCE: II-1

Acute uterine bleeding, unrelated to pregnancy, can be defined as excessively heavy or prolonged bleeding of uterine origin sufficient in volume as to require urgent or emergent intervention. It is a relatively common clinical condition that is a source of distress for patients, a challenge for health care providers, and a substantial drain on health care resources, because many of these women are managed with inpatient surgical procedures.[1] Acute uterine bleeding can present in the context of chronic abnormal uterine bleeding, or in women who have heretofore experienced normal menstrual function. Therapy has typically consisted of one or a combination of surgery and pharmacologic therapy, but data regarding the relative frequency of use of these interventions is currently unavailable. Surgical options for acute bleeding can include dilation and curettage,[2] uterine artery embolization,[3] endometrial ablation,[4–7] and hysterectomy. Medical management can consist of estrogens alone,[8] progestins alone,[9] or estrogens plus progestins in the form of combination oral contracep-

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tives. Support for the use of combination oral contraceptives for acute bleeding comprises only a combination of textbook recommendations[10] and expert opinion.[11–13] Despite their widespread use, however, there exists a paucity of information regarding the effectiveness, side effects, and patient satisfaction associated with the commonly used medical regimens.[14]

Our objective was to compare the efficacy of multidose regimens based upon an orally administered progestin and a monophasic combined oral contraceptive in the treatment of hemodynamically stable women with nongestational, acute uterine bleeding.

MATERIALS AND METHODS

This study was an open-label, randomized clinical trial (RCT) performed on patients with acute uterine bleeding presenting to the Southern California Kaiser Permanente Los Angeles and West Los Angeles Medical Centers. Approval for the study was obtained from the institutional review board, the Kaiser Permanente Southern California Regional Research Committee. Patients were recruited from the emergency room, gynecology urgent care, and outpatient clinics between July 2003 and June 2005. Eligible participants were nonpregnant, hemodynamically stable, premenopausal women at least 18 years of age with acute uterine bleeding, which, in the opinion of the treating physician, required emergent medical or surgical intervention. Bleeding was not to be related to obvious structural defects identified on physical examination, or, if deemed appropriate by the treating clinician, by transvaginal ultrasound. Eligibility required the hemoglobin to be at least 8 g/dL Exclusion criteria included unstable vital signs, current or recent pregnancy, the use of an intrauterine contraceptive device, current infertility treatment, recent uterine surgery (within 6 weeks), and contraindications to estrogen therapy including, but not limited to, current smoking, a history of thromboembolic events, chronic liver disease, history of an estrogen-sensitive malignancy, and a history of adverse reaction to gonadal steroids.

Initial screening included a questionnaire to aid with the determination of eligibility and other baseline data, routine physical and gynecologic examinations to ensure that bleeding was emanating from the cervical canal, the measurement of hemoglobin, performance of a pregnancy test, and any other investigations deemed necessary by the provider. Pelvic ultrasound or endometrial biopsy or both were performed by the clinician if indicated but were not inclusion criteria. Patients who were bleeding from visible structural lesions such as cervical polyps or prolapsing leiomyomas were excluded. Eligible women were invited to participate in the study, and those who signed the approved informed consent document were consecutively enrolled. Enrollees were randomly assigned to receive either medroxyprogesterone acetate 20 mg three times daily for 7 days or an oral contraceptive (OC) containing norethindrone 1 mg and ethinyl estradiol (E2) 35 mg, administered 3 times daily for 7 days. Following the 7 days of therapy, patients continued with either medroxyprogesterone acetate 20 mg daily or norethindrone 1 mg and ethinyl E2 35 μg 1 tablet daily, respectively, for an additional 3 weeks (Fig. 1). Randomization was performed using sequentially numbered, sealed then shuffled, opaque envelopes containing one of the two assignments created in blocks of 10 each with an equal opportunity for receiving each intervention.

After enrollment in the study, patients were given an information sheet specific to their assigned medication, a worksheet, and a 2-week follow-up appointment date. Each enrolled patient was instructed to use the worksheet to record daily pill taking, uterine bleeding, pad and tampon counts, and specific side effects or accompanying symptoms, including bloating, nausea, and pain. Subjects could withdraw from the study at any time to seek additional treatment. The worksheet and patient's response to treatment was assessed at the 2-week face-to-face visit by the study coordinator who was not blinded to the treatment allocation. The 4-week follow-up could be by office visit or telephone interview.

The primary outcome of the trial was avoidance of unscheduled surgery in the 28-day follow-up period. Additional outcomes included days to cessation of bleeding, pad and tampon counts, patient satisfaction scores, and the degree of ancillary symptoms such as cramping and side effects associated with the medication, such as nausea and bloating. Such symptoms, as well as overall patient satisfaction with the treatment received were assessed with 5-point Likert scales. Symptoms were recorded using the following scale: 0–none, 1–mild, 2–moderate; 3–severe; 4–unbearable. Satisfaction was also recorded on a 0–4 scale where "0" was very unsatisfied and "4" was very satisfied. Information on subsequent surgery was primarily obtained from the patient's electronic medical record that allowed access to any of the 12 Kaiser Foundation medical centers in the Southern California region. Patients were also questioned regarding subsequent surgery at the time of the 2- and 4-week

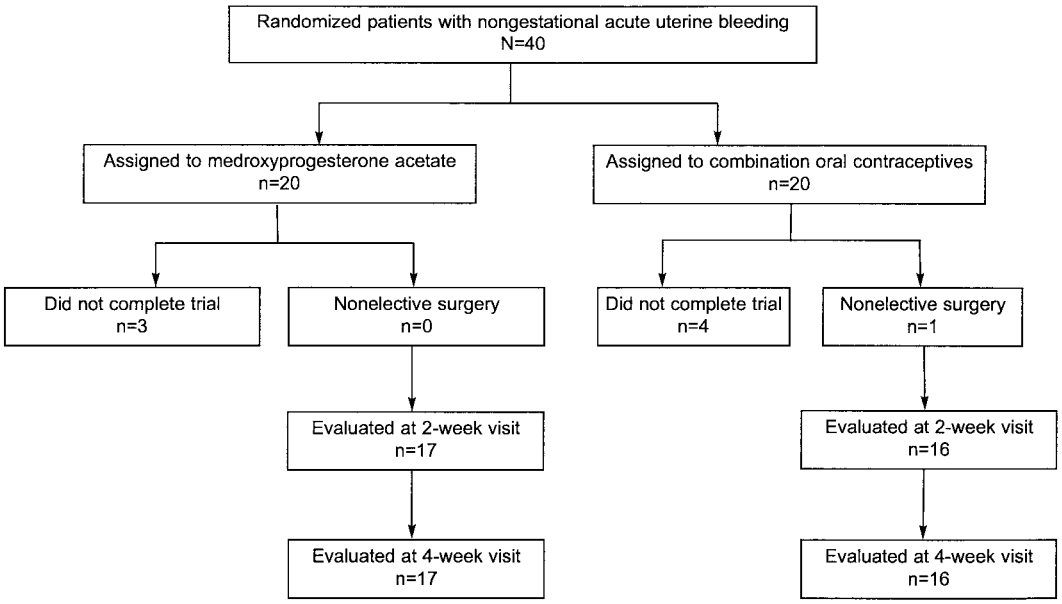

Fig. 1. Participant flow. Those randomly assigned to oral contraceptives were instructed to take a pill containing ethinyl estradiol 35 μg three times per day for 1 week and then one pill daily for 3 weeks. Patients allocated to medroxyprogesterone acetate (medroxyprogesterone acetate) were asked to take 20 mg three times per day for 1 week then 20 mg per day for the subsequent 3 weeks.

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visits in the event that surgery was performed outside of the system.

A sample-size analysis was performed before the start of the study to assess the number of subjects needed to demonstrate equivalence between the treatment regimens. A difference of 20% or less in efficacy measures between the two groups would define clinical equivalence.[15] To test, with 80% power, a *P* value of .05, and 95% confidence interval (two-tailed test), 188 subjects were required. Thus, 200 subjects would be needed to account for an estimated 10% attrition rate.

Statistical analysis was based on the intention-to-treat principle unless otherwise stated. Statistical software used for analysis was SAS 9.1 (SAS Institute Inc., Cary, NC). Wilcoxon rank sum tests were used for categorical variables and Fisher exact tests were applied to continuous variables as appropriate. All significance tests were 2-tailed, with an α level of 0.05.

RESULTS

Forty eligible women were enrolled in the trial between July 2003 and June 2005. Twenty patients were randomly assigned to each treatment group. Preenrollment pelvic ultrasound was performed in three patients (medroxyprogesterone acetate–2; OC–1) and pretreatment endometrial biopsies in four patients (medroxyprogesterone acetate–4; OC–0). Seventeen (85%) of the medroxyprogesterone acetate group and 16 (80%) of the oral contraceptive group completed all study visits and submitted study diaries for the 2- and 4-week visits (P=1.000). In the first week, 16 of the patients in the medroxyprogesterone acetate group documented compliance with therapy, with three patients recording four missed doses. One patient did not complete the dosing component of the study diary. Of the 15 OC patients who completed the dosing component of the study diary, four documented missing a total of 24 doses. It is not possible to adequately evaluate the compliance with therapy or the clinical outcomes associated with seven patients who did not return for follow-up and who did not respond to multiple telephone calls. However, the medical record was available for these patients, allowing an assessment for hospital admission and the use of operating rooms in any of the 12 Southern California Kaiser Permanente medical centers.

There were a number of barriers to recruitment in our two institutions. A number of clinicians were biased to one treatment or another and did not want patients entered into the trial. There were a number of patients as well who selected one treatment or the other or who did not want to complete the necessary documentation required by the protocol. Some patients had clearly identifiable cervical lesions or prolapsing leiomyomas that excluded them from partic-

ipation. Finally, there were relatively large numbers of women who did not meet the inclusion criteria because of recent use of gonadal steroids.

Initial demographic and clinical characteristics were similar in the two groups (Table 1). Clinical outcomes are shown in Table 2. All of those receiving medroxyprogesterone acetate and 95% of the OC patients avoided an unscheduled surgical procedure during the 4-week treatment period. One patient in the OC group underwent a nonelective dilation and curettage for acute bleeding. No nonelective procedures for uterine bleeding in the 4-week interval were found in the medical records of the seven patients who did not return for followup.

The median number of days to cessation of bleeding was 3 in both in the medroxyprogesterone acetate and the OC group (P=.400). Cessation of bleeding by the 2-week visit was reported by 76% of evaluated patients in the medroxyprogesterone acetate group compared with 88% in the OC group. When those who did not complete the study were included in the analysis (intention to treat) and were assumed to be treatment failures, bleeding cessation rates fell to 65% and 70%, respectively (Table 2).

Mean treatment satisfaction scores (Table 2) were similar for both groups (medroxyprogesterone acetate 3; OCs 3). Four of the medroxyprogesterone acetate group (23.5%) and five of the OC group (31.2%) reported "satisfaction" scores of 0 or 1, suggesting that they were unsatisfied with the therapy. Eighty-one percent of the medroxyprogesterone acetate group and 69% of the OC group said that they would use the medication again for bleeding if needed (Table 2). Median scores for bloating, cramping, and nausea did not differ significantly between the groups, either at baseline or during treatment (Table 3). When the symptoms data were analyzed within each treatment group, there was a statistically significant drop in the nausea scores between week 1 and week 2 of treatment (P=.008) in the combined oral contraceptive group. This relationship was not seen in the medroxyprogesterone group.

DISCUSSION

In this study both medroxyprogesterone acetate in the multidose regimen tested and multidose, monophasic, combination oral contraceptives containing 1 mg of norethindrone and 35 μg of ethinyl E2 seemed to be effective treatment for nongestational acute uterine bleeding in hemodynamically stable patients. There was a low incidence of emergent use of the operating room in both treatment groups. Compliance with the therapeutic regimen seemed less in the OC group. However, and although the mean side effect scores were low, a substantial number of subjects were unsatisfied with the intervention and would not use the therapy again.

The side effect profiles were similar between the two groups despite the oft-held clinical impression that combination estrogen–progestin oral contraceptives are associated with more nausea and medroxyprogesterone acetate with increased bloating. However, the observation that there was less compliance with OC therapy during the first week suggests that estrogen-mediated side effects may be more substantial than suggested from the symptom scores. The observations regarding reduced nausea comparing multidose and single dose ethinyl E2-norethindrone might not persist should the study be repeated with a larger number of patients. However, if found to be consistent, they could explain the subjective impressions by both providers and patients that multidose combination oral contraceptives cause more nausea and vomiting.

Table 1. Demographic and Baseline Characteristics (Intent-to-Treat Population)

Demographic Characteristics	MPA (n=20)	OCP (n=20)	*P*
Median age (y)	44.5	42.5	.159
Race [n (%)]			.402
Hispanic	9 (45)	10 (50)	
African American	3 (15)	5 (26)	
White	4 (20)	3 (16)	
Asian	1 (5)	2 (11)	
Other	3 (15)	0	
Mean BMI	30.3	29.0	.635
Mean duration of current bleeding episode (d)	15.5	8.0	.100
Mean Hb (g/dL)	12.4	12.8	.476
Mean no. pads in previous 24 h	4.5	5.0	.692
Mean no. tampons in previous 24 h	0	0	.690

MPA, medroxyprogesterone acetate; OCP, oral contraceptive pill; BMI, body mass index; Hb, hemoglobin.
Continuous variables were analyzed with Wilcoxon rank sum test. Race was analyzed using χ^2 tests.

Table 2. Study Outcomes by Treatment Group (As Evaluated Unless Stated)

Outcome	MPA "Treatment"	OCP "Control"	RR (95% CI)
Avoidance of emergent procedure (%)	100 (20)	95 (20)	1.05 (0.88–1.33)
Cessation of bleeding (%)	76 (17)	88 (16)	0.87 (0.56–1.31)
Cessation of bleeding (ITT)* (%)	65 (20)	70 (20)	0.92 (0.54–1.48)
Days to bleeding cessation	3 (17)	3 (16)	.400
Patient satisfaction (0, very unsatisfied, to 4, very satisfied)	3 (16)	3 (16)	.880
Would use medication again (%)	81 (16)	69 (18)	1.18 (0.73–.98)

MPA, medroxyprogesterone acetate; OCP, oral contraceptive pill; RR, relative risk; CI, confidence interval; ITT, intention to treat.
Figures in parentheses are number of participants.
* Intention-to-treat analysis assuming those lost to follow-up did not stop bleeding.

Table 3. Ancillary Symptoms and Treatment Side Effects

Symptom (Median of Average)	MPA	OCP	*P*
Bloating			
Baseline	0	0	.444
Week 1	0.00	0.00	.851
Week 2	0.00	0.00	.567
Cramping			
Baseline	1	1	.745
Week 1	0.00	0.43	.496
Week 2	0.00	0.00	.754
Nausea			
Baseline	0	0	.269
Week 1	0.00	0.57*	.710
Week 2	0.00	0.00	1.000

MPA, medroxyprogesterone acetate; OCP, oral contraceptive pill.
Scored from 0=none to 4=unbearable.
* Statistically significant compared with week 2 by signed rank test.

We performed a systematic search of the available literature in all languages, looking for publications relating to the medical treatment of acute uterine bleeding in nonpregnant women. In MEDLINE and MEDLINE RCT we searched from January 1966 to May 31, 2006 using the following terms: Acute Uterine Bleeding, Menorrhagia, Hypermenorrhea, Dysfunctional Uterine Bleeding, Abnormal Uterine Bleeding, Heavy Uterine Bleeding, and von Willebrand Disease. In the Cochrane Database of Systematic Reviews the same search terms were applied to Issue 1, 2006.

The only previously published clinical trial reporting the use of progestins alone for the treatment of nongestational, acute uterine bleeding was published in 1997. Aksu et al[9]studied the effectiveness of medroxyprogesterone acetate in 24 adolescents who were hospitalized with excessive uterine bleeding and anemia. Patients were given 60–120 mg of medroxyprogesterone acetate day 1, followed by 20 mg per day to a total of 10 days. All of the patients stopped bleeding within 4 days; 25% on day 1 and 29%, 21%, and 25% on days 2, 3, and 4, respectively.

There is only one published report evaluating the effectiveness of an unopposed parenterally administered estrogen regimen for the treatment of nongestational acute uterine bleeding. In a randomized, double blind, placebo-controlled trial of 34 patients conducted by DeVore et al,[8] either placebo solution or a solution containing intravenous conjugated equine estrogens was administered to women with acute uterine bleeding. At five hours, bleeding had stopped in 72% of the patients who received intravenous conjugated equine estrogens and in 38% who received placebo (P=.021).

The fact that we did not have a placebo group is a potential study weakness. In the 5-hour RCT comparing unopposed intravenous conjugated estrogens to placebo previously described, 38% of those assigned to placebo stopped bleeding within 5 hours.[8] However, this was an "in hospital" study using infused agents that had a 5-hour time horizon. For outpatient, orally-based therapy the risks of developing significant anemia in an untreated group made the use of a placebo-controlled trial potentially unethical.

It is accurate to say that the patients who qualified for this clinical trial are likely heterogeneous with respect to the cause of the abnormal uterine bleeding. However this is a study on women with acute bleeding who are not pregnant and who do not have an externally visible lesion (on speculum examination). Given the relatively high body mass index, one could infer that the frequency of anovulatory abnormal uterine bleeding may be relatively high. Regardless, we believe that this is a group recognizable to clinicians and one in whom it is difficult, impracticable, and perhaps inappropriate to evaluate the specific cause in detail given the acuity of the situation. After cessation of bleeding with the acute interventions described, the clinician will then have the opportunity

and ability to perform the needed investigations for chronic abnormal bleeding if indeed it is present.

Our literature search identified no previously published trials describing or evaluating the combination of an estrogen and a progestin in acute uterine bleeding, although it is apparent that oral contraceptives are used commonly for this indication in everyday practice. It is also the only randomized trial to compare two medical therapies for nongestational acute uterine bleeding. The sample size was insufficient to demonstrate actual equivalence between the treatment regimens; however no statistically significant difference in efficacy was shown in this study. Because relatively high-dose oral medroxyprogesterone acetate may be an effective treatment alternative for patients with acute bleeding, it may have particular value for those in whom estrogens are poorly tolerated or contraindicated.

The selection of medications, dose, and scheduling were based upon textbook recommendations, the author's personal experience and, with respect to medroxyprogesterone acetate, the available predicate literature. It seems quite possible, if not likely, that other progestins and alternative combination oral contraceptive formulations would also be effective, but the design and scope of this small trial precludes any comments on other formulations. Given the incidence of women who did or may have discontinued therapy and of those unwilling to take the medication again, it may be worthwhile to evaluate other progestin and estrogen-progestin formulations for both efficacy and patient tolerance, Other agents, such as tranexamic acid, shown to be effective in the treatment of chronic heavy menstrual bleeding, have theoretical value for acute uterine bleeding in nonpregnant women and should also be considered in the design of future clinical trials.

Both multidose oral medroxyprogesterone acetate and a multidose regimen of ethinyl E2 and norethindrone combination oral contraceptives, in the doses described, may be effective and, reasonably well tolerated for the treatment of nongestational acute uterine bleeding. However, the sample size of this trial is too small either to confirm such an impression or to prove equivalence of the two formulations and administration regimens. Larger randomized trials should be designed both to confirm these impressions and to evaluate other formulations and administration schedules.

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