Original Article

DOI: 10.7860/JCDR/2016/18178.7891

A Comparative Study to Evaluate the Efficacy of Vaginal vs Oral Prostaglandin E_1 Analogue (Misoprostol) in Management of First Trimester Missed Abortion

Obstetrics and Gynaecology Section

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ABSTRACT

Introduction: Missed miscarriages, occurring in upto 15% of all clinically recognized pregnancies are a cause of concern for the patients. Though many researchers in the past have compared the surgical and medical approaches in management of such patients, only a few have executed an appraisal of two routes of misoprostol at equal dosages in treatment of first trimester missed miscarriages.

Aim: To compare the efficacy of misoprostol by vaginal and oral route, for the management of first trimester missed abortion; and to recognize the utility of misoprostol for cervical dilation prior to any surgical termination of pregnancy.

Materials and Methods: A randomized prospective trial, comparing the efficacy of misoprostol, by vaginal and oral routes, for termination of first trimester missed abortion was conducted in the Department of Obstetrics and Gynecology, Government Multi-Specialty Hospital, Chandigarh over one year. Hundred subjects satisfying the inclusion criteria from 213 consecutive women presenting to the institute with first trimester missed abortion were hospitalized. The study participants were randomly assigned to one of the two treatment groups, using sequentially numbered envelopes, to receive 400mcg misoprostol vaginally or orally to a maximum of three doses six hours apart, and outcome documented. Patients were followed up on Day 14 and 6 weeks after discharge. Primary outcome evaluated was drug-induced complete expulsion of Products of Conception (POCs). Secondary outcomes measured were induction expulsion interval, number of doses required, classification of failures, cervical canal permeability in women requiring surgical evacuation, side effects, hemoglobin drop, duration and amount of post-abortal bleeding, time of resumption of menses, experience with side effects, patient satisfaction and acceptability to treatment.

Results: Both routes were highly effective (vaginal=92%, oral= 74%, p=0.032), safe and acceptable with tolerable side effects. The mean time to expulsion was longer (13.24hrs) in the oral than vaginal group (10.87hrs). All 4 unsuccessful cases in vaginal group and 12 of 13 in oral group had permeable cervices prior to surgical evacuation. Most women labeled the side effects as tolerable in both the groups. Overall acceptance rate to treatment was high in both the groups A and B (76% and 70%).

Conclusion: Vaginal misoprostol is more effective than oral misoprostol for first trimester missed abortion.

Keywords: Gestational sac, Missed miscarriages, Surgical evacuation

INTRODUCTION

Missed miscarriages in the first trimester are characterized by the arrest of embryonic or fetal development with ultrasound findings of an empty gestational sac or an embryo/fetus without cardiac activity [1]. They occur in upto 15% of all clinically recognized pregnancies [2]. Most of these occur spontaneously, but some pregnancies simply stop growing without obvious symptoms, with a deferment in expulsion of conceptus. An escalating percentage of these cases are now diagnosed on routine first trimester ultrasound scanning [3,4].

The presence of a non-continuing pregnancy is upsetting to mother, besides being a considerable human and financial burden [3]. A woman with missed miscarriage, especially recurrent one, usually presents as an anxious, infuriated individual on the verge of despair.

Surgical evacuation remains gold standard of care, being quick and highly effective, when performed by a proficient provider in appropriate setting. However, the associated complications have coxswained incessant attempts to search for alternate suitable management strategies [5].

Expectant management has downsides of ambiguity in timing of expulsion and need for surgical backup. Therefore, the thrust today is being budged towards utilizing medical methods to beget a trudging non-traumatic cervical dilatation, separation of products and their expulsion [6-9].

Prostaglandins (PGs) by various routes have transfigured the treatment of missed miscarriage. Use of PGs alone is rationalized by the innate plummet in progesterone brought about by death of the conceptus. Surgical maneuvers are resorted to, if products of conception are not ousted. However, surgical procedure then becomes innocuous and easy because of cervical priming, separated products and thick contracted myometrium. Considerable savings in resources can thus be made if routine curettage can be circumvented by adopting a medical approach.

Misoprostol is PGE_1 analogue (15- deoxy, 16- hydroxy, 16-methyl PGE_1) extensively used for termination of pregnancy, despite it being an “off label use” [10-13], since it is effective, inexpensive, with long shelf life (2 years) at room temperature, and requiring no needles for administration. It also has fewer side effects than PGE_2 analogues [9]. Though it is active both by oral and vaginal routes, most women favour oral route to evade the unpleasant vaginal examination. Following oral administration, plasma concentration of active metabolite of misoprostol-misoprostol acid reaches the zenith in 30 minutes and wanes nippily then on. Uterine contractility initially increases and then plateaus one hour later. Vaginal application is

found to be superior and is believed to lessen the gastrointestinal side effects; it results in slower increase and lower peak plasma concentration of misoprostol acid than oral administration, but overall drug concentration reaching target organ is higher in vaginal route [14].

Though few studies have been conducted till date to evaluate and compare efficacy of oral and vaginal routes of misoprostol in missed miscarriage, very few researchers have juxtaposed the drug at equal dosages [15,16], especially in India. Keeping this in mind, the present study was planned to compare safety and efficacy of 400µg misoprostol administered orally and intravaginally in missed abortion upto 12 weeks period of gestation. It was also proposed to identify the utility of misoprostol for cervical dilation prior to any surgical procedures that could be applied routinely in the outpatient department patients. It thus had to determine if medically induced termination of missed miscarriage is a realistic alternative to surgery.

MATERIALS AND METHODS

It was a randomized prospective trial, conducted in Government Multi-Specialty Hospital, Chandigarh, India after getting ethical clearance over a span of one year from July 2013 to June 2014. Two hundred thirteen consecutive women attending the hospital, with missed miscarriage ≤12 weeks of gestation were assessed for inclusion into the study.

Inclusion Criteria

(i) Females of age group 18-45 years; (ii) Gestational age ≤ 12 weeks by last menstrual period (LMP); (iii) Diagnosis of missed abortion on USG; (iv) Mild vaginal bleeding or spotting per vaginum; (v) Closed cervix on bimanual pelvic examination; (vi) Haemoglobin ≥9gm/dl; (vii) Axillary temperature <37.5 degree C; (viii) No history of inflammatory bowel disease, asthma, liver disease or contraindication to use of misoprostol; (ix) Place of residence within 100 km from of the hospital; (x) Willingness and ability to give informed consent; (xi) Willingness to abstain from intercourse for first 14 days of study; (xii) Willingness to comply with follow-up schedule

Exclusion Criteria

(i) Women <18 years or >45 years of age; (ii) Fetal gestational age >12 weeks; (iii) Any degree of cervical dilatation; (iv) Excessive uterine bleeding; (v) Haemoglobin concentration<9gm/dl); (vi) Haemodynamic instability; (vii)Blood pressure ≥160/90 mmHg; (viii) Poor general health of any cause; (ix) Deranged coagulation profile (defined as PTI≤85%) (x) Signs or symptoms of infection; (xi) Maternal history of asthma or cardiac disease or cerebral disease; (xii) Use of anticoagulants or H/O any bleeding disorder; (xiii) Known allergy to or C/I to misoprostol use; (xiv) Active lactation; (xv) Any prior medical or surgical treatment to interrupt current pregnancy; (xvi) Twin gestation sac; (xvii) Molar pregnancy; (xviii) Inability or refusal of patient to adhere to follow-up.

Hundred eligible women were hospitalized and ultrasonographic confirmation of missed abortion was obtained. Their baseline investigations were carried out. If woman's blood group was Rh negative, she was given prophylactic anti D immunoglobulin 50µg intramuscularly. Women were then randomly assigned to one of the two regimens, using computer generated sequentially numbered envelopes, to receive 400µg oral or vaginal misoprostol.

GROUP A: Fifty women were administered 400µg of misoprostol intravaginally into posterior fornix (soaked in normal saline solution), repeated six hourly up to a maximum of three doses. Vaginal cleansing had been performed before insertion with 10% povidone iodine (Betadiene). Following insertion, women were asked to remain in fully recumbent position for three hours.

GROUP B: Fifty women were dispensed 400µg of oral misoprostol, repeated every six hours for a maximum of three doses. Women swallowed the pills with sips of water in presence of the doctor.

All patients were monitored for vitals, vaginal bleeding and expulsion of POCs and information chronicled about drug side-effects. Over the next 18-30 hours, complete, incomplete or no expulsion was documented. At every dosing interval, each female was enquired about expulsion of POCs and of possible symptoms. If POCs had been expelled, it was examined grossly. Also, a bimanual pelvic examination was performed to determine any retained gestational material. If POCs had been left, administration of further doses of misoprostol was continued until the tissue was expelled completely or maximum dose of misoprostol had been given. If patient aborted earlier completely, no further doses were given.

Before beginning the study, the following clinical outcomes had been defined: a) Success was defined as non-surgical evacuation of POCs confirmed by absence of echogenic structure measuring≥15mm in AP diameter on USG; b) Failure was defined as any recourse to surgical abortion; c) Abortion was considered incomplete when POC was not completely expelled or the echogram was not an archetypal image of an empty uterine cavity.

The outcome was documented 12 hours after the last dose of misoprostol to facilitate sufficient time for the drug to be effective. Surgical evacuation was performed in case of heavy vaginal bleeding, severe pain or infection and in patients who failed to abort or abort completely even then. Women were also allowed to request a surgical termination at any time if they did not wish to continue or to wait for complete evacuation. The patients were observed for a period of 6 hours after complete abortion or surgical evacuation and then discharged. They received prophylactic antibiotics and analgesics for 5 days.

All women were then asked to return to hospital 14 days post discharge when they underwent bimanual pelvic examination, USG and an interview to assess quantity of post-abortal bleeding {in duration as brief (<5 days), average (5-10 days), or prolonged (>10days), and in amount, as heavy (>periods), moderate (=periods) or mild (<periods)}, and to determine each woman's experience with side-effects or any additional treatment taken. Any patient who initially had expelled, but afterwards presented with excessive bleeding, intrauterine remains, infection, excessive pain, was reassessed and subjected to surgical evacuation. Therefore, the initial estimation of success in those cases was then changed to failure, because of recourse to surgery. Winikoff et al., classification was used for itemization of failure cases [17].

The second follow-up visit was scheduled at 6 weeks to determine the time taken for resumption of menses, any other side effects (if experienced) and overall acceptability to treatment. However, all women were advised to return to hospital at any time if any complications or questions arose.

STATISTICAL ANALYSIS

To detect a significant difference from 95-90% efficacy among the two groups, with a power of 80%, and incidence of first trimester missed miscarriage being 10-20%, two-tailed of 5% required a minimum of 50 women in each group, thus achieving a sample size of 100 (as deduced through "Epi info package" software. Data was recorded on predesigned proformas and analysed using available SPSS (Statistical package for social sciences) software version 19.0 for Windows, after application of appropriate statistical tests. p-value <0.05 was considered significant.

RESULTS

Demographic and maternal characteristics [Table/Fig-1]: Mean age of patients was 23.7± 3.9 years (ranging from 16-36 years). Majority of cases hailed from rural areas (74%) belonging to lower socioeconomic status (37%-Class IV, 29%-Class III). Maximum

Baseline characteristics	Vaginal (Group A) (n=50)	Oral(Group B) (n=50)	p-value
Age (years) (Mean ± SD)	23.7± 3.9SD	23.9± 3.7SD	0.668
Parity			0.771
Primigravida	34 (68%)	36 (72%)	
Multigravidas	16(32%)	14(28%)	
Gestational age (weeks)			
<6 weeks	3 (6%)	1(2%)	0.960
6-12 weeks	47(94%)	49(98%)	
Previous spontaneous abortion	18(36%)	17(34%)	0.997
Previous cesarean section	8(16%)	10(20%)	
SE status I	2 (4%)	1 (2%)	0.945
11	4(8%)	3(6%)	
111	15(30%)	14(28%)	
1v	17(34%)	20(40%)	
v	12(24%)	12(24%)	
BMI (Kg/m^2) mean	21.713	22.155	0.183

[Table/Fig-1]: Demographic and baseline maternal characteristics

women were housewives (78% in Group A and 72% in Group B). The mean BMI of patients was 21.713 ± 2.2017 kg/m^2 in Group A and 22.155 ± 1.8281 kg/m^2 in Group B. Most patients were Primigravida in both groups (68% in Group A and 72% in Group B), and amongst remaining, 36% women in Group A and 34% in Group B had previous abortion. The mean gestation age was 68.84 days±1.468 in Group A and 68.74±1.348 days in Group B.

Clinical outcome and its relationship with number of doses of misoprostol: In Group A, success rate was 92% as against 74% in Group B [Table/Fig-2]. Amongst these, 5 (10%) patients in Group A and 0 in Group B expelled completely with single dose. Another 17 (36.96%) in Group A and 9 (24.32%) in Group B expelled after two doses [Table/Fig-3]. Vaginal administration of misoprostol was thus found to be more effective than oral for complete uterine evacuation (p=0.032)

Outcome	Group A (Vaginal) n (%)	Group B (Oral) n (%)
Success	46 (92)	37 (74)
Failure	4 (08)	13 (26)
Total	50 (100)	50 (100)

[Table/Fig-2]: Clinical outcome

Number Of Doses	Group A n (%)	Group B n (%)
One	5 (10.87)	0 (0)
Two	17(36.96)	9 (24.32)
Three	24 (52.17)	28 (75.68)
Total	46 (100)	37(100)

[Table/Fig-3]: Relationship of number of doses and outcome in successful cases

Induction-Expulsion Interval [Table/Fig-4]: Mean I-E interval (in hours from administration of first dose to complete expulsion)was 10.87±3.49 hours in Group A and 13.24±3.1 hours in Group B, difference being statistically highly significant (p-value=0.0032)

Failures: Four patients in Group A failed treatment. Out of these, abandonment of drug schedule and subsequent recourse to surgical manoeuvre was required in 1 woman (owing to severe hyperpyrexia), while remaining were incomplete abortions. In Group B, 13 patients failed treatment, amongst which, surgical evacuation was performed on request in 1 patient, while other 12 cases had retained products.

Cervical Canal Permeability in Failures [Table/Fig-5]: All 4 (100%) unsuccessful cases in Group A and 12 of 13 (92.8%) in Group B had permeable cervices prior to surgical evacuation.

I-E Interval (hrs)	Group A n (%)	Group B n (%)
≤6	5 (10.87)	0 (0)
7-12	19 (41.31)	15 (40.54)
13-18	21(45.65)	20 (54.05)
>18	1(2.17)	2 (5.41)
Total	46 (100)	37 (100)
Mean	10.87	13.24
Standard Deviation	3.49	3.10
Standard Error of Mean	0.52	0.51

[Table/Fig-4]: Induction- expulsion interval

Cervical Permeability (Ability to pass No. 8 Hegar's dilator)	Group A n (%)	Group B n (%)
Permeable	4 (100)	12 (92.31)
Non-Permeable	0 (0)	1 (7.69)
Total	4 (100)	13 (100)

[Table/Fig-5]: Classification of failures

Side effects and Complications [Table/Fig-6]: All side effects of misoprostol were more common with oral group (the difference was statistically insignificant; p-value=0.965).

Post-abortal bleeding [Table/Fig-7]: Heavy bleeding was observed in 26% of women in Group A and 22% in Group B; the duration for which bleeding lasted varied between 5-10 days following expulsion in both groups (p=0.377).

Time of resumption of menstruation [Table/Fig-7]: Maximum females (56% in Group A and 58% women in Group B) had normal restoration time of 30-45 days (p=0.925).

Experience with side effects [Table/Fig-8]: Most women labeled the side effects as tolerable in both groups (p=0.965).

Side-Effects	Group A n (%)	Group B n (%)
Nausea/Vomiting (Requiring anti-emetics)	30 (60)	36 (72)
Dizziness	10 (20)	12 (24)
Headache (Requiring analgesics)	09 (18)	12 (24)
Severe Crampy Pain (Requiring analgesics/ anti-spasmodics)	15 (30)	24 (48)
Diarrhea	6 (12)	7 (14)
Fever with chills (requiring anti-pyretics)	2 (4)	4 (8)
Excessive bleeding	1(2)	3 (6)
Discharge per vaginum	1 (2)	2 (4)
Cervical tear	0 (0)	0 (0)
Uterine Rupture	0 (0)	0 (0)
Death	0 (0)	0 (0)

[Table/Fig-6]: Incidence of side-effects and complications

Characteristic	Group A n (%)	Group B n (%)	p-value
Amount of post abortal bleeding			
Heavy(>periods)	11(22)	13 (26)	0.828
Moderate (=periods)	30 (60)	27 (54)	
Mild (<periods)	9 (18)	10 (20)	
Duration (Days) of post abortal bleeding			
Brief (<5)	04 (08)	03 (06)	
Average (5-10)	28 (56)	26 (52)	0.799
Prolonged (>10)	18 (36)	21 (42)	
Time of Resumption of Menstruation			
<30 days	13 (26)	12 (24)	0.925
30-45days	28 (56)	29 (58)	
>45 days	9 (18)	9 (18)	

[Table/Fig-7]: Other Follow-up visit parameters

Acceptability	Group A n (%)	Group B n (%)
Satisfaction		
Satisfied	38 (76)	35(70)
Unsatisfied	9 (18)	11 (22)
Neutral	3 (6)	4 (8)
Would choose again	41 (82)	39 (78)
Would recommend to others	39 (78)	37 (74)

[Table/Fig-8]: Patient satisfaction and acceptability to treatment

Patient satisfaction and acceptability to treatment [Table/Fig-8]: Overall acceptance to treatment was high in both groups A and B (76% and 70%) (p-value=0.792).

DISCUSSION

In the present research, patients were of younger age-group as compared to American and European studies [3-7,10,17-22], thus, reflecting early age at marriage and first conception widely prevalent in India. Most of the study participants were illiterate, hailing from rural background and lower socioeconomic status, engaged in household work, with normal BMI. All these observations substantiated the section of society attending the institute for its gynecological problems. The mean gestational age was 68.84 $\pm$ 1.468 days in Group A and 68.74 $\pm$ 1.348 days in Group B, highlighting later detection of missed miscarriage as opposed to the data from the Western countries. This may be ascribed to low acceptability of USG during first trimester in our society.

In our study, final success rate was defined as a complete uterine evacuation without the need for surgical intervention for any reason, including ET of 15mm (as assessed by TVS). This increased our success rates when compared to most studies in literature, without increasing the burden on health facilities [3,16,23,24].

Ninety two percent and 74% success rates in Group A and Group B exemplify that misoprostol is an effective non-surgical method with high success in missed miscarriage, with higher overall efficacy of vaginal route. This further supported the hypothesis that antigestagens are not really necessary for termination of missed miscarriage because progesterone levels are usually low, and therefore only PGs are required to initiate uterine contractions and expulsion of gestational sac.

The wide variation (13%-100%) in success rates of misoprostol [Table/Fig-9] may be attributed to several reasons: route of administration, different dose schedules, repeated dose schedule, stretching the follow-up (waiting for 3-15 days was found to be associated with higher success rates), patient selection, type of PG analogue used like sulprostone or PGE_2 analogues along with misoprostol or simultaneous use of mifepristone in other studies, small sample size causing bias, use of USG before starting treatment is associated with higher success, criteria used to define success (waiting period of 24 hours or more, cut-off for ET presumed to be 15 mm or till 30mm to rule out RPOC).

The proportion of patients aborting within 12 hours was significantly higher in Group A than in Group B. These findings of smaller mean I-E interval in vaginal group, were in consonance with work by most of the authors [16,25,28,30]. However, it was lower than that attained by Carbonell et al., which could be credited to larger dose used by latter in their work [28]. Since efficacy of medical method depends upon the dose, number of doses, route of drug administration and dosing interval, we recommend increasing the number of doses and decreasing the dosing interval, which would possibly lead to increased cumulative effects of misoprostol. Increasing the waiting period after the administration of last dose before documenting expulsion would also increase the expulsion rates. Also, use of more objective parameters in study would be instrumental in increasing the efficacy of medical management. Use of serum β HCG levels for demonstrating complete expulsion as opposed to USG would decrease the possibility of surgical curettage in patients with thickened endometrium even if they have otherwise completely aborted. Similarly, if serum β HCG has not declined by 50% compared to baseline, passage of pregnancy is not said to be complete.

Unlike other studies, most women (3 out of 4 in Group A, and 12 out of 13 failures in Group B) underwent surgical evacuation for incomplete abortion. Also, even in women who failed treatment, we observed permeable cervices during evacuation (ability to pass no. 8 Hegar's dilator). These observations were even better than those attained by previous researchers [4,30,31] reinforcing the utility of misoprostol for cervical dilation prior to any surgical maneuvers that could be applied routinely in the outpatient department patients.

In our study, incidence of GI side effects was higher in oral group, but was easily managed using anti-emetic and anti-diarrheal drugs. The most noteworthy side effect associated with misoprostol had been diarrhea, which is a natural response of intestinal smooth muscles to increased level of PGs, and it is usually mild and self-limiting, resolving within a few days despite continued therapy. Exploration for newer drug formulations for misoprostol is warranted in near future to increase the efficacy of oral route. Also, the drug should be dosed with meals to minimize its GI side effects. Hyperpyrexia, requiring antipyretics, was observed in 8% of our subjects in Group B (oral) and 4% in the Group A (vaginal). Dizziness (20% vs 24%), headache (18% vs 24%) and discharge

SNo.	Study	Study Design	Dose of Misoprostol used (µg)	Number of Subjects	Success rates
1	Creinin MD et al., (1997) [18]	Oral vs Vaginal	800 vs 1600	20	25% vs 88%
2	Zalanyi S (1998) [20]	Vaginal	800	25	88%
3	Carbonell et al., (1999) [25]	Vaginal	3000	720	89.4%
4	Pang MW et al., (2001) [26]	Oral vs Vaginal	800	201	64.4% vs 61.1%
5	Wood SL et al., (2002) [27]	Vaginal	1600	50	80%
6	Ngoc NTN et al., (2004) [28]	Oral vs Vaginal	800	200	89% vs 92.9%
7	Betsy T, Habeebullah S (2004) [16]	Vaginal	800	60	76.7%
8	Panditrao SA et al., (2005) [19]	Vaginal	800	84	88.09%
9	Nguyen TNN et al., (2005) [29]	Oral	1200	300	94.6%
10	Bique C et al., (2007) [15]	Oral vs Surgical	600	270	91% vs 100%
11	Scott G Petersen et al., (2013) [10]	vaginal	400 or 800	264	77.7%
12	Current Study (2014)	Vaginal vs Oral	400 x 3	100	92% vs 74%

[Table/Fig-9]: Comparative success rates of treatment in missed miscarriage using different routes and doses of misoprostol.

per vaginum (2% vs 4%) were reported more in our study due to unspecified reason. In our study, no woman had cervical tear, uterine rupture or death following the management. These inferences were far better than those by most of the investigators [2,10,16,19,20,28,31-34]. Use of scoring systems, like the visual analogue scale for pain scoring, to evaluate adverse effects would certainly decrease the wide subjective variability in reporting and their subsequent over estimation of side effects. However, additional studies are necessitated to find out the optimal dose so that this more acceptable route could be used with results comparable to vaginal route.

Heavy post-abortal bleeding was observed in very few women (11 in group A and 13 in Group B) increasing acceptability to medical treatment, underpinning it as a suitable alternative to surgical evacuation.

Maximum women {28 (56%) in Group A and 29 (58%) in Group B} had normal restoration of menstruation within 30-45 days emphasizing that the effect of misoprostol on onset of first menstruation following abortion is not dependent on route. However, further studies with larger sample size are desirable to validate our inferences.

Most women in both the groups, reported side effects to be 'tolerable', and only few characterized them as 'bad'. Satisfaction rate in both groups was high (76% in Group A, 70% in Group B). In Group A, only 9 (18%) were not satisfied, mainly because they found repeated vaginal application awkward. In Group B, 11 (22%) subjects were disgruntled with treatment because of failure, side effects and time taken. But when asked about future use and recommendations, 82% and 78% in vaginal and oral groups would choose the method again, and 78% in vaginal and 74% in oral group would recommend to their friends. The treatment can also be imparted on a domiciliary basis which could increase the woman's convenience and privacy, ensuring increased compliance and further reducing the cost of medical management.

CONCLUSION

This initial experience with the medical management of first trimester missed miscarriage is consistent with the published literature. The results of the present study endorse the utilization of misoprostol, either vaginally or orally, as a practical alternative to conventional surgical evacuation in missed miscarriage with high success rates, patient acceptability and tolerable side effects. Vaginal route is more efficacious. However, it should be offered only by well-trained clinicians who can provide surgical treatment in the event of failed abortion or excessive bleeding. Even in cases who fail to expel, use of misoprostol makes the surgical procedures much easier due to its cervical ripening effect.

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FINANCIAL OR OTHER COMPETING INTERESTS: None.

Date of Submission: **Dec 04, 2015**
Date of Peer Review: **Feb 26, 2016**
Date of Acceptance: **Apr 02, 2016**
Date of Publishing: **May 01, 2016**