Transvaginal cervical length scans to prevent prematurity in twins: a randomized controlled trial

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Use of routine transvaginal cervical length measurement in twins did not change the gestational age at delivery.

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Back Ground: Twin pregnancies are associated with an increased risk of perinatal morbidity and mortality primarily due to spontaneous preterm deliveries. The mean gestational age for delivery is 35.3 weeks and twins account for 23% of preterm births less than 32 weeks. A number of strategies have been proposed to prevent preterm deliveries; tocolytics, bed rest, hospitalization, home uterine activity monitoring, cerclage, and most recently, progesterone. Unfortunately, none have proven effective. Recent meta-analyses and reviews suggest that transvaginal cervical length (TVCL) ultrasound in the second trimester is a powerful predictor of preterm birth among asymptomatic women. Indeed, TVCL has the highest positive and negative predictive values for determining the risk of spontaneous preterm delivery in twin pregnancies. It follows that TVCL assessment may allow identification of a subset of twin pregnancies who are better candidates for interventions intended to prevent prematurity.

Objective: To determine whether use of transvaginal cervical length prolongs gestation in twin pregnancies.

Study Design: This is a multicenter, randomized, controlled trial of 125 dichorionic or monochorionic/diamniotic twin pregnancies without prior preterm birth <28weeks. The study group (n = 63) had transvaginal cervical length and digital exams monthly from 16-28 weeks and were managed with a standard algorithm for activity restriction and cerclage. The control group (n=62) had monthly digital cervical examinations but no routine transvaginal cervical length ultrasound examinations. The primary outcome was gestational age at delivery. Secondary outcomes included percentage of deliveries < 35 weeks, maternal and neonatal outcomes.

Results: The mean gestational age at delivery was 35.7 weeks (95% CI: 35.2 to 36.2) among those managed with transvaginal cervical length and 35.5 weeks (95% CI: 34.7 to 36.4) among the control patients. As shown in Figure 2, the Kaplan-Meier estimates of deliveries before 38 weeks were not significantly different between groups. This was true whether we compared curves with a log-rank test ($p = 0.67$), Breslow test ($p = 0.67$), or Tarone-Ware test ($p = 0.64$). The percentage of deliveries before 35 0/7 weeks did not differ: 27.4% for subjects managed with routine transvaginal cervical length and 28.6% (RR = 0.96, 95% CI: 0.60 to 1.54). Our study had an 80% power to detect a 12 day difference in the gestational age at delivery with 95 percent confidence.

Conclusions: The overall mean length of gestation and the percentage of women delivering prior to 35 weeks did not differ between twin gestations managed with transvaginal cervical length and digital exams monthly from 16-28 weeks with a standard algorithm for activity restriction and cerclage and controls who had monthly digital cervical examinations but no routine transvaginal cervical length. Routine second trimester transvaginal ultrasound assessment of cervical length is not associated with improved outcomes when incorporated into the standard management of otherwise low risk twin pregnancies.

Keywords: Prematurity prevention, Transvaginal cervical length, Twins

INTRODUCTION

Twin pregnancies are associated with an increased risk of perinatal morbidity and mortality primarily due to spontaneous preterm deliveries. The mean gestational age for delivery is 35.3 weeks and twins account for 23% of preterm births less than 32 weeks.¹ A number of strategies have been proposed to prevent preterm deliveries; tocolytics, bed rest, hospitalization, home uterine activity monitoring, cerclage, and most recently, progesterone.

Unfortunately, none have proven effective.

Recent meta-analyses and reviews suggest that transvaginal cervical length (TVCL) ultrasound in the second trimester is a powerful predictor of preterm birth among asymptomatic women.^{2,3} Indeed, TVCL has the highest positive and negative predictive values for determining the risk of spontaneous preterm delivery in twin pregnancies.⁴ It follows that TVCL assessment may allow identification of a subset of twin pregnancies who are better candidates for interventions intended to prevent prematurity.

Retrospective studies designed to assess the clinical utility of TVCL in the prevention of prematurity among twin pregnancies have yielded conflicting results. Michaels and colleagues compared the outcomes of twin pregnancies managed with transabdominal cervical length ultrasound to an historic control group managed without such ultrasound and both perinatal mortality and prematurity were decreased.⁵ Conversely, Gyamfi and colleagues compared the outcomes of twin pregnancies managed with TVCL to those of controls without exams and noted no differences in gestational age at delivery or the rate of preterm birth.⁶

Given the encouraging predictive values of TVCL and the conflicting results from retrospective studies, we designed a randomized controlled trial to assess the utility of routine TVCL in the prevention of prematurity among twin pregnancies. The primary hypothesis was that twin pregnancies managed with the information gained from TVCL ultrasound would have a greater length of gestation and fewer preterm deliveries.

MATERIALS AND METHODS

Between December 2002 and June 2006, we performed a multicenter, randomized, controlled trial at three United States military hospitals. The study was approved by the Institutional Review Board and ethics committee at each hospital. Informed consent was obtained on all subjects.

All twin pregnancies at less than 20 weeks were identified by ultrasound and referred for screening and possible recruitment. The subjects were either active duty members or military dependents. Because of frequent military moves, if individuals moved (learned of move after randomization) we planned to contact the new physician, inform them of the study and ask for continued management according to our protocol (with subject consent) and obtain data for inclusion in the analysis.

Prior to randomization, subjects received counseling about the risks of prematurity and the possibility of a benefit to TVCL assessment in the prevention of preterm birth. Subjects were excluded if they had any of the following: 1) history cervical insufficiency with plans for a

history-indicated cerclage; 2) a history of possible cervical insufficiency with plans to perform serial transvaginal cervical length; 3) a prior preterm delivery < 28 weeks; 4) preexisting plans to relocate and deliver at a different hospital; 5) discovery of a lethal fetal congenital anomaly, confirmation of aneuploidy, monoamniotic twins or twin-twin transfusion syndrome prior to enrollment; or 6) age < 18. If not excluded, randomization was conducted with the use of a random number table in permuted blocks of six using opaque, sequentially numbered sealed envelopes at a central site. The study group was defined as the group assigned to have routine TVCL studies. A nurse who was trained in prematurity prevention counseled all participants in both groups and provided preterm labor educational handouts.

Scheduled visits occurred at 15-16, 19-20, 23-24, and at 27-28 weeks for all women. As was our practice, a gentle digital examination of the cervix was performed at each of these visits. Subjects randomized to the study group underwent TVCL either by one of the investigators or a trained sonographer and a set protocol was followed as described by Dr Iams.⁷ All images were reviewed by the first author to ensure correct measurements were obtained. Based on the results of the TVCL, all women in the study group were managed according to a standard algorithm (Table 1). In addition, to the scheduled exams, TVCL were allowed if subjects presented with preterm labor.

Subjects in the control group were managed without the use of routine TVCL. In addition, use of this exam was discouraged in symptomatic women except for specific indications: symptoms of cervical insufficiency to include heavy vaginal discharge or bleeding at 16-22 weeks or for evaluation of bleeding to evaluate for placenta previa. Likewise, no transabdominal evaluation

the cervix was performed. No standardized protocol was established for the management of this group. The decision to perform a cerclage or alter activity status was left to the managing clinicians. Women who were placed at bed rest for preterm labor were also contacted weekly by a nurse. Subjects in the control group received a single blinded TVCL at 23-24 weeks in order to compare the mean cervical length between the 2 groups. Both the women and the managing physicians were blinded to the results and the exam was not performed by these physicians.

In order to minimize confounders, both groups were seen by the same providers and efforts were made to keep management identical except for the use of the TVCL. The diagnosis and management of preterm labor was standardized with the exception that women in the study group were allowed to have TVCL. The timing and use of steroids for asymptomatic individuals was based on either the TVCL protocol or was left to the discretion of the managing obstetrician. Planned deliveries prior to 38 weeks were discouraged. Women who declined participation in the study or who were ineligible received care similar to the control group unless the reason for the exclusion required serial TVCL scans.

The primary outcome was gestational age at delivery. Since planned deliveries of twins were common at 38 weeks and to ensure that this did not affect the primary outcome, all subjects who delivered after this time were recorded as a delivery at 38 0/7 weeks.

We recorded data regarding demographics, risk factors, type of twin placentation as determined by ultrasound, and evidence of twin-twin transfusion. Additional maternal outcomes included the number of days of bed rest, number of hospital days, use of tocolytics, and administration of

steroids for fetal lung maturity. Neonatal outcomes included birth weight, length of stay in the neonatal intensive care unit, and occurrence of a predefined composite measure of severe morbidity. When comparing neonatal outcome, twin A and twin B were compared separately. In addition to quantitative measures of gestational age, preterm births were categorized as due to spontaneous or medically indicated.

All analyses were performed by intention to treat. Interval data were compared with an unpaired t test or Mann-Whitney U test and categorical data were compared with the X^2 test or Fisher exact test depending on the cell size. For the primary outcome we planned to construct Kaplan-Meier survival curves for gestational age at delivery. The threshold for statistical significance for all tests was set at $p < 0.05$. All statistical procedures were performed using IBM SPSS Statistics for MAC Version 22 (IBM).

For the primary outcome of gestational age at delivery, we estimated that 45 subjects would be needed in each group to detect an improvement from 36.5 to 38 completed weeks of gestation with 95% confidence and a power of 0.80. With IRB approval we added additional subjects to explore a secondary outcome, preterm delivery prior to 35 weeks. We estimated that an additional 20 patients would be needed in each group to detect a 50% reduction in the number of deliveries before 35 weeks with the same confidence and power.

RESULTS

Of 153 women with twin pregnancies < 20 weeks who were evaluated for participation in the study, 125 were randomized (Figure 1). There was one withdrawal and one relocation; both were

in the control group. With their consent, the outcomes for both were obtained and included in the analysis. One protocol violation occurred. A control subject was found to have a short cervix during her blinded exam at 23 weeks. The sonographer inappropriately notified the woman and her physician. She was subsequently managed with bed rest at home and delivered at 36 6/7 weeks. Based on intention to treat, she was still analyzed with the control group.

There were no differences in the demographic or clinical characteristics in the two groups (Table 2). Ninety-eight subjects were randomized at Wilford Hall, 20 at Wright Patterson, and 7 at Madigan Medical Center and the percentage randomized to the 2 groups was not statistically different (data not shown). Participants had few other significant risk factors for preterm delivery; only one subject smoked, 4 subjects (2 in each group) had a history of a prior preterm delivery between 28 and 36 6/7 weeks and 5 (2 in the control and 3 in the TVCL group) had a history of prior cervical surgery.

The mean gestational age ($\pm$ SD) at delivery for the entire study was 35.6 ± 2.7 weeks with a range of 25.6 to 39 weeks. The mean gestational age at delivery was 35.5 weeks (95% CI: 34.7 to 36.4) among the control patients and 35.7 (95% CI: 35.2 to 36.2) among those managed with TVCL. As shown in Figure 2, the Kaplan-Meier estimates of deliveries before 38 weeks were not significantly different between groups. This was true whether we compared curves with a log-rank test, Breslow test, or Tarone-Ware test. Among control subjects 17/62 (27.4%) delivered before 35 weeks compared to 18/63 (28.6%) among those managed with TVCL (RR = 0.96, 95% CI: 0.60 to 1.54). We found no differences in any of the secondary outcomes (Table

3). These results were unchanged if women with medically indicated deliveries were excluded (data not shown).

No differences in neonatal outcomes were noted between the groups. We also found no differences in the overall rate of admission or days spent in the NICU (data not shown). Four neonatal deaths and one stillbirth occurred. The stillbirth occurred in the TVCL group at 22 weeks following a laser ablation for twin-to-twin transfusion. Three neonatal deaths occurred in the control group and all were associated with medically indicated preterm deliveries. The only neonatal death in the TCVL group was a newborn with Down syndrome and severe hydrops.

Only one subject in the treatment arm was noted to have a TVCL of < 2.0 cm at < 24 weeks of gestation. Two women in the TVCL group received cerclages. One was placed due to a cervical length of 1.1 cm at 18 weeks. This patient delivered at 35 5/7 weeks due to spontaneous preterm labor. The other individual had an emergency cerclage placed at 22 weeks when she presented with symptoms with increased vaginal discharge and pelvic pressure. She was found to be completely effaced and 3 centimeters dilated. An emergent modified Shirodkar cerclage was placed and she remained at hospital bed rest until 34 weeks and delivered at 39 weeks. No patient in the control group received a cerclage.

Of the 62 subjects in the control group, 55 had a blinded TVCL at 23-24 weeks of gestation. In the TVCL group, 61 of 63 subjects had this exam. The mean cervical length for each group was similar (controls 3.7 ± 0.9 cm versus 3.5 ± 0.8 cm in the TVCL group ($p = 0.22$)). Thirteen women in the control group and 11 women in the TVCL group had medically indicated preterm

deliveries. Excluding these individuals and those who did not have an exam done, the percentage of women with a cervical length ≤ 3.5 cm was similar in each group with 18/43 (41.8 %) in the control group and 24/50 (48%) in the TVCL group ($p = 0.55$). If only those subjects with shorter cervixes are examined, the median gestational age at delivery was slightly greater in the TVCL group but this difference was not significant (36.7 versus 36.0, $p = 0.67$). In addition, there was no significant difference in the percentage of these women delivering prior to 35 weeks (data not shown).

The number of women in each group who received various interventions was also similar (Table 4). When analysis of the various interventions is limited to the subgroup of women with short cervixes (≤ 3.5 cm) at 23-24 weeks, no difference in the various interventions was noted (data not shown).

COMMENT

In our study the routine use of TVCL combined with a standardized management approach to the women with a short cervix did not prevent prematurity among twin pregnancies. This was true whether comparing the effect on mean gestational age at delivery or the rate of preterm delivery before any specific gestational age. In our study the use of routine TVCL measurements did not improve neonatal outcomes. Furthermore, we were unable to show any benefit in preventing or avoiding maternal interventions by utilizing this measurement. With the added strength of a prospective trial and standardized approach to those subjects with cervical shortening, our study

suggests that routine TVCL ultrasound does not have a role in the routine management of twin pregnancies at this time.

Other investigators have examined whether routine protocols for the management of twins can prevent prematurity. In one retrospective cohort study, Ellings et al demonstrated a reduction in perinatal morbidity, birth weights less than 1500 grams, and NICU admissions among women managed in a specialized twin clinic with standardized management guidelines compared to women managed outside of such an approach.⁸ In that study, women were given detailed preterm labor education and had digital cervical exams with the determination of a cervical score and a set protocol for gradations of activity restrictions. Conversely, Edwards and colleagues noted no differences in prematurity rates among twin gestations managed in a standard preterm labor prevention clinic compared to a general prenatal clinic.⁹ Both of these studies were retrospective and conducted at a time before TVCL ultrasound was widely practiced.

Our study updates older reports and suggests that despite including routine TVCL ultrasound, our ability to prevent preterm birth among twin gestations remains limited. It is disappointing that with such a powerful predictor of prematurity, we were unable to make a difference in gestational age at delivery and associated adverse outcomes. Among several possible explanations for our results, the most likely is that at this time there are no effective therapies for the prevention of prematurity among twin gestations, even among those identified with a short cervix. Unfortunately, interventions such as cerclage and weekly injections of 17-hydroxyprogesterone that have proven to be effective in preventing preterm birth among some high-risk singleton pregnancies have failed when studied in randomized controlled trials among

twin gestations.^{10,11} In addition, a recent meta-analysis has suggested that use of cerclage in multiple gestations may actually double the risk of PTD.¹² Our study suggests that much like these therapies, routine TVCL ultrasound as applied in our group is of limited utility among twin gestations.

Our study has several limitations. First, the size was too small to detect differences in the rate of prematurity at more extreme and potentially consequential gestational ages. It is possible that the benefit of ultrasound indicated cerclage is the prevention of extremely preterm or previable birth. Owen and colleagues noted that while surveillance and indicated cerclage did not impact the rate of delivery prior to 35 weeks among women with a prior preterm birth, it did decrease deliveries prior to 24 completed weeks and overall perinatal mortality largely due to these early deliveries.¹³ Based on our results, we would need almost 10 times the number of subjects in each arm to examine the reduction in births at less than 32 weeks, a time when the consequences of prematurity are arguably much greater.

Another limitation is that our study does not permit a direct estimate of the effect of cerclage for a short cervix among twin gestations. Importantly, only 2 cerclages were performed in women in the TVCL group. We were surprised that we only detected one patient in the study group with a cervix less than 2.0 cm. Observational ultrasound studies of twin pregnancies suggest that the rate of cervical shortening less than 2.0 cm at a similar gestational age is between 5% - 17.5%.^{15,16} Retrospective studies also suggest a higher utilization of cerclage among twin pregnancies so monitored with transvaginal ultrasound. Newman and colleagues prospectively followed 128 twin gestations with TVCL and offered cerclage to the 21 (16.4%) with a cervical

length less than 2.5 cm.¹⁶ While these authors noted no improvement in preterm birth with cerclage, their selection of patients for the intervention was more liberal than ours. We based our decision to offer cerclage only to those with a cervix less than 2.0 cm in part on their suggestion. At least one randomized controlled trial has demonstrated that cerclage may be most effective at much shorter cervical lengths such as 1.5 cm.¹³ Ideally, certification of sonographers would have been done at a central location but all sonographers were made aware of the correct imaging technique and a set protocol was followed as described by Dr Iams.⁷ Next, our population is generally healthy with few additional risk factors for preterm delivery. This was a middle class population with a low incidence of prior preterm deliveries, sexually transmitted disease (data not shown), smoking and coexisting medical problems. Further evidence that this population was low-risk is the low perinatal morbidity and mortality seen in entire study. Finally, including monochorionic diamniotic twin pregnancies may have biased and limited the generalizability of the study because of the relatively high frequency of twin-twin transfusion syndrome within this population of twins (n=7 or 5.6% of the entire cohort). Since these twin pregnancies did not develop this syndrome until after randomization they were included. This subgroup accounted for a number of the preterm deliveries (3 of 6 deliveries prior to 30 weeks) and it is less likely that information obtained from a TCVL will improve outcomes in this high-risk subset of twins. However in order to exclude this subset of twins a much larger study would be needed.

We acknowledge that the incorporation of other interventions not included in our approach may have the potential to alter the results of a similarly constructed trial. Since completion of this study, two randomized trials have demonstrated a significant reduction in preterm birth among

women with a short cervix who were treated with vaginal progesterone compared to those treated with placebo.^{17,18} In a small subset of patients from their study, Fonseca and colleagues reported a non-significant reduction in preterm birth among twin pregnancy with TVCL less than or equal to 1.5 cm.¹⁷

In summary, we have demonstrated that routine TVCL is not associated with improved outcomes when incorporated into the standard management of otherwise low risk twin pregnancies. While transvaginal ultrasound remains a strong predictor of prematurity in twin pregnancies, effective interventions to prevent these preterm births remain elusive. Routine TVCL ultrasound for uncomplicated twin pregnancies should remain an investigational tool at this time.

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Table 1: Management guides for study group

Cervical length	Management
>3.5 cm	Routine obstetrical care
3.0-3.5 cm	Reduced physical activity
2.0-2.9 cm	Reduced physical activity and weekly contact with nurse
<2.0 cm less than 24 0/7 wks EGA	Modified Shirodkar cerclage, indomethacin for 48 hours, 5 days of hospital admission, bedrest at home and weekly contact with nurse
<2.0 cm over 24 0/7 wks EGA	Betamethasone for fetal lung maturity, indomethacin for 48 hours, 5 days of hospital admission, bedrest at home and weekly contact with nurse

Table 2: Baseline demographic and clinical characteristics

Demographics	Cervical Length Group (n = 63)	Control Group (n= 62)
Age (years)	31.37 $\pm$ 5.4	29.66 $\pm$ 5.1
Gravidity	2.6 $\pm$ 1.5	2.5 $\pm$ 1.4
Married (%)	95.2%	93.5%
Initial BMI	24.5 $\pm$ 4.7	24.8 $\pm$ 4.5
Height (inches)	64.7 $\pm$ 2.4	65.01 $\pm$ 2.8
Total weight gain (pounds)	43.75 $\pm$ 31.6	39.6 $\pm$ 15.8
Education (years)	15.2 $\pm$ 2.4	15.2 $\pm$ 2.5
Working (%)	54%	65%
Children < 6 years old at home	26 (41%)	23 (37%)
Dichorionic Placentation	88.5%	81%
Infertility treatment		
IVF	19 (30.2%)	19 (30.6%)
None	34 (54%)	36 (58%)
Other	10 (16%)	7 (11%)
Preexisting medical conditions	6 (9.5%)	12 (19.4%)
Twin-twin transfusion (n)	2	5

Data presented as mean $\pm$ standard deviation unless otherwise indicated

Interval data were compared with an unpaired *t* test and categorical data with the X^2 test or Fisher exact test depending on the cell size.

Table 3: Perinatal Outcomes

	Transvaginal Cervical Length Ultrasound Group (n = 63)	Control Group (n= 62)	Statistical Significance
Mean EGA at Delivery	35.5 weeks (95% CI: 34.7 to 36.4)	35.7 (95% CI: 35.2 to 36.2)	
Delivery < 30 weeks ^a	1 (1.6%)	5 (8.1%)	$p = 0.12$
Delivery < 32 weeks ^a	4 (6.3%)	7 (11.3%)	$p = 0.36$
Delivery < 34 weeks ^a	10 (15.9%)	16 (25.8%)	$p = 0.19$
Delivery < 35 weeks	17 (27.4%)	18 (28.6%)	$p = 0.96$
Weight at delivery: twin A (g)	2496 $\pm$ 525	2341 $\pm$ 677	$p = 0.16$
Weight at delivery: twin B (g)	2419 $\pm$ 556	2243 $\pm$ 635	$p = 0.16$
Admitted to NICU (twin A)	25 (39.7%)	24 (38.7%)	$p = 1.0$
Admitted to NICU (twin B)	27 (42.9%)	21 (33.9%)	$p = 0.359$
Composite morbidity (twin A) ^b	2 (3.2)	7 (11.3%)	$p = 0.10$
Composite morbidity (twin B) ^b	6 (9.5)	7 (11.3%)	$p = 0.78$

Data presented as mean $\pm$ standard deviation unless otherwise indicated. Interval data were compared with an unpaired t test and categorical data with the X^2 test or Fisher exact test depending on the cell size.

^a Indicates post hoc analyses.

^b Composite morbidity included one or more of the following: neonatal death, mechanical ventilation after 72 hours of life, chronic lung disease, grade 3 or 4 intraventricular hemorrhage or periventricular leukomalacia, necrotizing enterocolitis, stage 3 or higher retinopathy of

prematurity, culture proven sepsis, or hemodynamic instability requiring pressor medications after 72 hours of life.

Table 4: Maternal interventions

	Transvaginal Cervical Length Ultrasound Group (n = 63)	Control Group (n= 62)	Statistical Significance
Activity restriction for preterm labor	34 (54%)	23 (40.4%)	$p = 0.07$
Activity restriction (total)	38 (60%)	30 (48.4%)	$p = 0.14$
Hospitalized for preterm labor	21 (33.3%)	16 (25.8%)	$p = 0.36$
Hospitalized for other reasons	13 (20.6%)	16 (25.8%)	$p = 0.49$
Received steroids for fetal lung maturity	20 (31.7%)	25 (40.3%)	$p = 0.49$
Received tocolysis	19 (30.2%)	14 (22.6%)	$p = 0.32$
Cerclage placed	2 (3.2%)	0	$p = 0.5$

Interval data were compared with an unpaired t test and categorical data with the X^2 test or Fisher exact test depending on the cell size.

FIGURE CAPTIONS

Figure 1: CONSORT Flow Diagram

Figure 2: Kaplan-Meier survival curve

Curve showing difference in time to delivery in patients with twin pregnancies managed with (green line) and without (blue line) routine transvaginal cervical length assessment with ultrasound. (Log Rank test, $p = 0.67$, Breslow test, $p = 0.67$, Tarone-Ware test, $p = 0.64$) Mean gestational age at delivery (controls), weeks: 35.5 (95% CI: 34.7 to 36.4). Mean gestational age at delivery (TVCL group), weeks: 35.7 (95% CI: 35.2 to 36.2).

Consolidated Standards of Reporting Trials (CONSORT)*

Table. Checklist of Items to Include When Reporting a Randomized Trial.

Section and Topic	Item #	Descriptor	Reported on Page #
<i>Title and Abstract</i>	1	How participants were allocated to interventions (eg, "random allocation," "randomized," or "randomly assigned").	3
<i>Introduction</i>			
Background	2	Scientific background and explanation of rationale.	5
<i>Methods</i>			
Participants	3	Eligibility criteria for participants and the settings and locations where the data were collected.	5, 6, 12
Interventions	4	Precise details of the interventions intended for each group and how and when they were actually administered.	7-9
Objectives	5	Specific objectives and hypotheses.	5
Outcomes	6	Clearly defined primary and secondary outcome measures and, when applicable, any methods used to enhance the quality of measurements (eg, multiple observations, training of assessors).	10
Sample size	7	How sample size was determined and, when applicable, explanation of any interim analyses and stopping rules.	11
<i>Randomization</i>			
Sequence generation	8	Method used to generate the random allocation sequence, including details of any restriction (eg, blocking, stratification).	7
Allocation concealment	9	Method used to implement the random allocation sequence (eg, numbered containers or central telephone), clarifying whether the sequence was concealed until interventions were assigned.	7
Implementation	10	Who generated the allocation sequence, who enrolled participants, and who assigned participants to their groups.	6, 7
Blinding (masking)	11	Whether or not participants, those administering the interventions, and those assessing the outcomes were blinded to group assignment. If done, how the success of blinding was evaluated.	N/A
Statistical methods	12	Statistical methods used to compare groups for primary outcome(s); methods for additional analyses, such as subgroup analyses and adjusted analyses.	11
<i>Results</i>			
Participant flow	13	Flow of participants through each stage (a diagram is strongly recommended). Specifically, for each group report the numbers of participants randomly assigned, receiving intended treatment, completing the study protocol, and analyzed for the primary outcome. Describe protocol deviations from study as planned, together with reasons.	Figure 1
Recruitment	14	Dates defining the periods of recruitment and follow-up.	5
Baseline data	15	Baseline demographic and clinical characteristics of each group.	12, 25
Numbers analyzed	16	Number of participants (denominator) in each group included in each analysis and whether the analysis was by "intention-to-treat." State the results in absolute numbers when feasible (eg, 10/20, not 50%).	11, 12
Outcomes and estimation	17	For each primary and secondary outcome, a summary of results for each group, and the estimated effect size and its precision (eg, 95% confidence interval).	13, 14, 26
Ancillary analyses	18	Address multiplicity by reporting any other analyses performed, including subgroup analyses and adjusted analyses, indicating those prespecified and those exploratory.	14, 15
Adverse events	19	All important adverse events or side effects in each intervention group.	13
<i>Comment</i>			
Interpretation	20	Interpretation of the results, taking into account study hypotheses, sources of potential bias or imprecision, and the dangers associated with multiplicity of analyses and outcomes.	15-17
Generalizability	21	Generalizability (external validity) of the trial findings.	18
Overall evidence	22	General interpretation of the results in the context of current evidence.	19, 20

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