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Per-protocol effect of earlier non-pneumatic anti-shock garment application for obstetric hemorrhage

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Synopsis

Earlier non-pneumatic anti-shock garment intervention was highly protective against maternal mortality and morbidity when analyzed to account for intervention fidelity; however, not all outcomes reached statistical significance.

Keywords

Hypovolemic shock; Maternal mortality; Maternal morbidity; Non-pneumatic anti-shock garment; NASG; Obstetric hemorrhage

Obstetric hemorrhage is the primary cause of maternal mortality worldwide, especially in lower-resource settings that are characterized by treatment delays [1]. The non-pneumatic anti-shock garment (NASG) is a first-aid device used to stabilize women in shock from obstetric hemorrhage until they can receive definitive care. The authors conducted a cluster-randomized trial (CRT) to evaluate NASG application at the primary health clinic prior to referral hospital transfer on maternal outcomes. Control participants received the NASG upon arrival at the referral hospital. The intent-to-treat analysis (ITT) reported a non-

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Conflict of interest
The authors report no conflict of interest.

statistically significant 46% reduction in mortality, 54% reduction in extreme adverse outcomes, and a significant 25% faster recovery from shock associated with earlier NASG intervention [2]. However, protocol violations occurred, potentially diluting the intervention effect. Thus, the effect of earlier NASG application was evaluated using 2 per-protocol analysis strategies.

The CRT was conducted between 2009 and 2012 in 38 primary health clinics referring to 5 referral hospitals in Zimbabwe and Zambia (clinicaltrials.gov: NCT00488462). The study protocol and methods are available elsewhere [2]. Institutional review boards affiliated with the following institutions reviewed and approved study and informed consent protocols: University of California, San Francisco; University of Zambia, Lusaka; University of Zimbabwe-UCSF Collaborative Programme on Health Research; and Department of Reproductive Health and Research, World Health Organization. Informed consent was obtained from all participants. Two per-protocol analysis strategies were explored. The first reassigned women by clinic-level protocol, moving 32 women who did not receive the NASG at the primary health clinic from the intervention to control group. The second reassigned women by full clinical protocol, reassigning the same 32 clinic patients to the control group and excluding 49 patients who did not receive the NASG at either the primary health clinic (intervention) or the referral hospital (control) per study protocol. Both groups excluded 2 women with unknown intervention receipt. Outcomes were mortality, morbidity, extreme adverse outcome (composite mortality and morbidity), and time to recovery, defined as return to normal shock index. We estimated random-effects logistic regression models for binary outcomes, and cox proportional hazards for time to event data, with robust sandwich variance estimator to account for the clustered study design. Data analysis utilized Stata version 12 (Stata Corp, College Station, USA).

One mortality was among the 32 women reassigned from the intervention to the control group. The first per-protocol strategy found earlier NASG intervention associated with a 60% reduced odds of mortality (OR 0.40; 95% CI, 0.10–1.67; P=0.213); a 65% reduced odds of extreme adverse outcome (OR 0.35; 95% CI, 0.09–1.37; P=0.131); and a significant 28% faster shock recovery (HR 1.28; 95% CI, 1.06–1.56; P=0.012) (Table 1). Further restricting the sample by the full clinical protocol, earlier NASG intervention had a 64% reduced odds of mortality (OR 0.36; 95% CI, 0.08–1.54; P=0.168); a 68% reduced odds of extreme adverse outcome (OR 0.32; 95% CI, 0.08–1.27; P=0.105); and a significant 28% faster shock recovery (HR 1.28; 95% CI, 1.05–1.57; P=0.015).

These results demonstrate the NASG to be highly protective against mortality, morbidity, and extreme adverse outcome; however, these results were still not statistically significant. Earlier NASG application was associated with a significantly faster shock recovery. Both per-protocol results demonstrate a stronger effect compared with the ITT results, since these women actually received earlier NASG application. ITT analysis is the dominant analysis paradigm for clinical trials to preserve the benefits of randomization; however, ITT results present the effect of an intervention as-assigned, which is problematic with incomplete intervention adherence. Where non-adherence occurs, particularly with a one-time, brief intervention with a large effect on mortality (such as the NASG), ITT results may not inform the true effect [3]. However, the per-protocol approach is prone to bias. We saw no

patterning in adherence by intervention group; however, it is possible that unmeasured confounding may have biased these estimates. Consideration of all NASG results is important for maternal health program and policy planners, and the clinical significance of the intervention as-received results should not be ignored. The results support NASG implementation at the primary health clinic level, within a continuum of care for obstetric hemorrhage.

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Table 1

Participant outcomes for per-protocol analysis of earlier NASG intervention, Zambia and Zimbabwe.

	Intervention		Control		OR	95% CI	*P* value
	No.	%	No.	%			
Per-protocol analysis strategy 1	(n=366)		(n=512)				
Survived with severe morbidity	0/366	0.0	1/501	0.2	-	-	-
Mortality	3/366	0.8	12/512	2.3	0.40	0.10–1.67	0.213
Extreme adverse outcome	3/366	0.8	13/501	2.6	0.35	0.09–1.37	0.131
Time to recovery[a,b]	165 (90–279)		209 (114–386)		1.28[d]	1.06–1.56	0.012
Per-protocol analysis strategy 2	(n=366)		(n=465)				
Survived with severe morbidity	0/366	0.0	1/463	0.2	-	-	-
Mortality	3/366	0.8	12/465	2.6	0.36	0.08–1.54	0.168
Extreme adverse outcome	3/366	0.8	13/463	2.8	0.32	0.08–1.27	0.105
Time to recovery[a,c]	165 (90–279)		209 (114–386)		1.28[d]	1.05–1.57	0.015

[a] Median (IQR).

[b] Intervention (n=303), Control (n=381).

[c] Intervention (n=303), Control (n=367).

[d] Hazard ratio.