Efficacy of Monsel Solution After Cervical Biopsy: A Randomized Trial

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Objectives: To estimate the efficacy and side effects of Monsel solution for hemostasis after cervical punch biopsy.

Methods: In a prospective, randomized trial, we compared application of Monsel solution versus a "wait and see" approach in women undergoing cervical punch biopsies in a 1:1 ratio. The primary end point was vaginal bleeding (VB) after 15 minutes measured by scoring a sanitary pad with a 5-level pictogram. Secondary end points were VB after 3, 6, and 24 hours (5-level pictogram), subjective estimation of overall VB during 24 hours, pain after 15 minutes and subjective estimation of overall pain after 24 hours, and overall satisfaction after 24 hours (11-level visual analogue scale).

Results: One hundred forty-five women were randomized between July 2015 and January 2016. Mean objective VB scores after 15 minutes in 75 women with Monsel solution were 1.2 ± 0.6 compared with 1.8 ± 1.0 in 70 women without Monsel solution ($P < 0.001$). The secondary end points VB after 3 and 6 hours, but not after 24 hours, were also in favor of Monsel solution (2.1 ± 1.1 vs 2.9 ± 1.2; $P < 0.001$; 1.6 ± 0.7 vs 2.2 ± 1.0; $P < 0.001$; 1.6 ± 0.9 vs 1.7 ± 0.9; $P = 0.4$, respectively). Subjective estimation of overall VB during 24 hours was lower for Monsel solution (23.2 ± 15.8 vs 35.9 ± 19.5; $P < 0.001$), but pain after 15 minutes, overall pain, and overall satisfaction were not significantly different between groups (19.2 ± 14.4 vs 17.9 ± 16.2; $P = 0.3$; 20.7 ± 15.8 vs 20.1 ± 18.0; $P = 0.5$; and 44.1 ± 21.5 vs 43.6 ± 23.2; $P = 0.9$, respectively).

Conclusions: Application of Monsel solution significantly reduces bleeding for 6 hours after cervical biopsy but does not affect overall pain or overall satisfaction.

Key Words: cervical dysplasia, colposcopy, hemostasis, Monsel solution, punch biopsy, randomized controlled trial

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Colposcopy is an integral part of cervical cancer screening.[1] In women with an abnormal Pap test or screening HPV result suggesting the presence of cervical intraepithelial neoplasia (CIN), colposcopy is performed for further diagnostic workup. Specifically, colposcopy is a means to visualize CIN lesions and allows for colposcopically guided cervical biopsies (CGCB). Colposcopically guided cervical biopsies are associated with vaginal bleeding (VB), pain, and discomfort. To achieve local hemostasis after CGCB, the application of Monsel solution is a widely used intervention.[2] The styptic effect of the solution is achieved through agglutination of proteins by ferric subsulfate.[3]

The use of Monsel solution after CGCB is based on data obtained in women undergoing cervical conization. For example, Lipscomb et al compared the vaginal application of Monsel solution to electrocautery after loop electrosurgical excision procedure (LEEP) and found no significant difference in blood loss.[4] Similarly, the application of Monsel solution after LEEP did not seem to result in less postoperative bleeding compared with not using Monsel solution.[5] Another trial investigated whether vaginal packing with Monsel solution or hemostatic sutures are more effective in reducing perioperative blood loss in women undergoing cold knife conization of the cervix. The authors found that vaginal packing with Monsel solution is superior to hemostatic sutures.[6] Because Monsel solution is effective in achieving local hemostasis after conization, it has been assumed that this intervention is also effective and useful after CGCB. However, there are no controlled data available guiding clinical practice regarding the application of Monsel solution after CGCB (PubMed search; March 19, 2016; search terms: punch biopsy, cervical dysplasia, colposcopy, bleeding, hemostasis, Monsel solution, colposcopically guided biopsy, randomized controlled trial). Therefore, we designed a prospective, randomized trial comparing the application of Monsel solution versus a "wait and see" approach in women undergoing CGCB for suspected cervical dysplasia. We hypothesized that the application of Monsel solution is noninferior to no application of Monsel solution regarding VB after 15 minutes with a noninferiority margin of 20%. Therefore, we chose VB after 15 minutes as the primary end point. Secondary end points were VB after 3, 6, and 24 hours; subjective estimation of overall VB during 24 hours; pain after 15 minutes and estimation of overall pain measured after 24 hours; and overall satisfaction after 24 hours. Assessing the efficacy and side effects of Monsel solution after CGCB is of clinical relevance because CGCB is a commonly performed procedure. Thus, the results of the present trial will have an impact on clinical practice.

METHODS

This prospective randomized trial was carried out at the Department of Obstetrics and Gynecology, Ruhr-Universität Bochum, Bochum, Germany, and the Institute of Cytology and Immune Cytochemistry ZYDOLAB, Dortmund, Germany, in a population of women referred to these institutions for colposcopy because of cervical abnormalities. Approval for this study was obtained by the ethics committee of the Ruhr-Universität Bochum (registration no. 5264–15; date of approval, May 7, 2015). The trial was registered with ClinicalTrials.gov (NCT02486471). The reporting of this study conforms to the CONSORT statement (SDC–CONSORT Checklist).[7] Informed consent was obtained from all women. We included women if they attended colposcopy for the first time and had an age between 18 and 80 years. Women were not allowed to participate if they had menstrual bleeding at the time of the examination. Also, we excluded women if they were pregnant or if they had a history of conization. Further exclusion criteria were presence of a language barrier, known coagulation disorder, the presence of severe renal or hepatic impairment, chronic pelvic pain, a concurrent analgesic medication, or the use of heparin or other blood coagulation inhibitors.

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Colposcopic examinations were performed by senior gynecologists with training in colposcopy. Colposcopy and CGCB were performed as follows: after visualization of the cervix, the tissue was evaluated in its native condition, and samples using a spatula for cytology and the DNAPap cervical sampler for human papillomavirus testing with the Hybrid Capture II Test (Qiagen, Gaithersburg, MD) were collected. The cervix was categorized as small or large. We considered a cervix to be small if it had a visually measured diameter less than 5 cm on a video colposcopy screenshot. In contrast, we considered a cervix to have a large size if it had a visually measured diameter equal or more than 5 cm. After applying a 3% acetic acid solution to the cervix for 1 minute, up to 4 CGCBs were taken from acetowhite lesions using a straight Tischler biopsy punch with a sharp tail. Endocervical curettage (ECC) was performed after punch biopsy. Lugol solution was not applied regularly. The colposcopic examination was assessed according to the 2011 colposcopic terminology of the International Federation for Cervical Pathology and Colposcopy.[8] Procedure duration was measured from the insertion to the removal of the vaginal speculum.

Randomization was performed immediately after CGCB. Women assigned to group 1 ("Monsel group") received local hemostasis using cotton swabs with an extra large head drenched in Monsel solution (20% ferric subsulfate), which were gently pressed on the bleeding areas of the cervix until no more bleeding was visible. Women assigned to group 2 ("wait and see") did not receive any hemostatic agents or other procedures, which could lead to hemostasis (eg, pressure on the biopsy site with a cotton swab). Instead, the examination was stopped directly, and the speculum was removed. All women received the same type of sanitary pad after examination.

The primary end point of the study was VB after 15 minutes measured semiquantitatively by scoring the sanitary pad with a modified 5-level pictogram (Figure 1). The VB was assessed by a study nurse who did not participate in the examination. At the same time, women scored their pain level using a horizontal 100-mm visual analogue scale (VAS) ranging from 0 ("no pain") to 10 ("worst imaginable pain"). Then, all women were issued a postpaid envelope with a questionnaire and 3 sanitary pads. Using this questionnaire, women scored the secondary end points VB after 3, 6, and 24 hours (measured by the same 5-level pictogram), subjective estimation of overall VB during 24 hours, estimation of overall pain after 24 hours, and overall satisfaction after 24 hours (all measured by an 11-level VAS [100 mm]) and sent the results back to the clinic by regular mail. The VAS ranged from 0 ("no bleeding") to 10 ("worst imaginable bleeding"), 0 ("no pain") to 10 ("worst imaginable pain",) and 0 ("maximally satisfied") to 10 ("maximally unsatisfied"), respectively. After each measuring of VB, women used a new sanitary pad.

Analysis was by intention to treat. All P values are 2-tailed, and a $P < 0.05$ was considered statistically significant. The sample size was calculated on the basis of the study hypothesis that application of Monsel solution is noninferior to no application of Monsel solution regarding VB after 15 minutes with a noninferiority margin of 20%. The assumption of a reduction of less than 20% of VB scores in women undergoing application of Monsel solution as compared with no intervention was based on previous personal experience, that is, a preliminary series of 6 women undergoing application of Monsel solution (n = 3) and nothing (n = 3). We assumed a risk of $\alpha = 0{\cdot}05$ (type I error) and $\beta = 0{\cdot}10$ (type II error) and a dropout rate of less than 5%. With 70 participants in each arm of the study using a 1:1 randomization, this study has a power greater than 80% to confirm noninferiority of the 2 study arms.

Using a block size of 4, a computer-generated random number series was contained within sequentially numbered closed opaque envelopes. The random allocation sequence was generated by a physician who did not take part in this study. Women were enrolled by 2 authors (Z.H. and C.B.T.). The envelopes were opened by the study nurse immediately after CGCB was completed. Women were blinded to the study group allocation.

Analysis was performed using parametric or nonparametric tests when data were normally distributed or skewed, respectively. Values are given as means ± standard deviations. We performed multivariate linear and logistic regression analyses with VB after 15 minutes or pain after 15 minutes as the dependent variables and age, parity, body mass index, procedure duration, biopsy volume, type of transformation zone, histological result, and group assignment ("Monsel solution" versus "wait and see") as the independent variables. We used the statistics software package SigmaPlot 12.5 (Systat Software Inc., San Jose, CA) for statistical analysis.

RESULTS

Approximately 166 patients were screened for this study. Fourteen patients did not meet the inclusion criteria and were therefore not included in the study (screening failures). Six patients declined to participate before randomization. In 1 patient, colposcopy was interrupted before randomization. All other patients screened and randomized for this study were included in

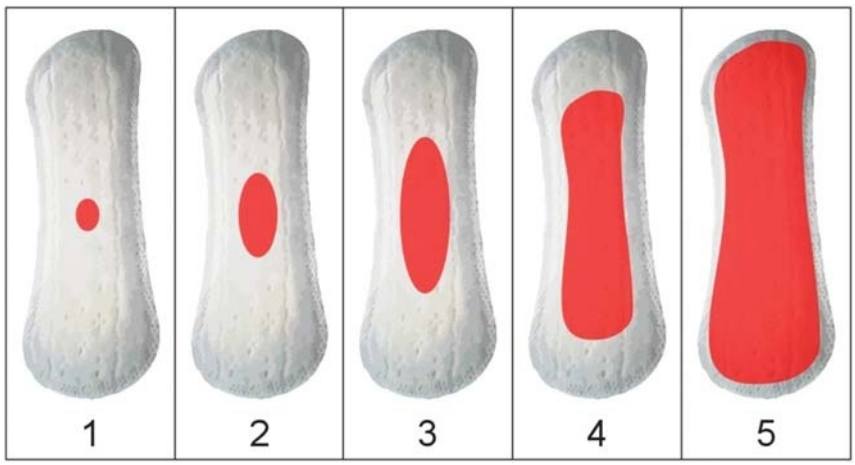

FIGURE 1. Five-level pictogram scale for measuring the amount of vaginal bleeding (VB).

the study and used for the intention-to-treat analysis. Thus, 145 patients undergoing CGCB for suspected cervical dysplasia were enrolled between July 2015 and January 2016. Patient characteristics according to study allocation (see Table, Supplemental Digital Content 1, http://links.lww.com/LGT/A35, which demonstrates the group-specific characteristics of study participants) were comparable between the 2 treatment groups. Seventy-five patients were randomized to arm 1 (application of Monsel solution), and 70 patients were randomized to arm 2 ("wait and see" approach). 123 of 145 (85%) patients mailed the questionnaire back to the study office and provided information on VB after 3, 6, and 24 hours and overall pain after 24 hours and subjective estimation of overall VB during 24 hours and overall satisfaction after 24 hours. A flow diagram depicting the patients' flow through the study is shown in Figure 2.

The histopathologic results of the CGCBs were as follows: 16 patients had CIN I, 25 patients had CIN II, 62 patients had CIN III, 2 patients had a microinvasive invasive squamous cell cancer (pT1a1), and 40 patients had no CIN in the specimen. One of those 40 patients had a melanocytic nevus.

Figure 3 (see also Table, Supplemental Digital Content 2, http://links.lww.com/LGT/A36, which illustrates the primary and secondary outcomes) shows a comparison of VB scores, pain scores, and satisfaction scores between the 2 groups. Specifically, in the intention-to-treat (ITT) analysis, the mean objective VB score after 15 minutes in 75 women with Monsel solution was 1.2 ± 0.6 compared with 1.8 ± 1.0 in 70 women without Monsel solution ($P < 0.001$). The secondary end points VB after 3 and after 6 hours were also in favor of Monsel solution (2.1 ± 1.1 vs 2.9 ± 1.2, $P < 0.001$; and 1.6 ± 0.7 vs 2.2 ± 1.0, $P < 0.001$, respectively). However, after 24 hours, the difference regarding VB was no longer statistically significant between the 2 groups (1.6 ± 0.9 vs 1.7 ± 0.9, $P = 0.4$). In accordance with the higher objective bleeding scores during the first 6 hours after CGCB, the subjective estimation of overall VB during 24 hours was also in favor of Monsel solution (23.2 ± 15.8 vs 35.9 ± 19.5, $P < 0.001$).

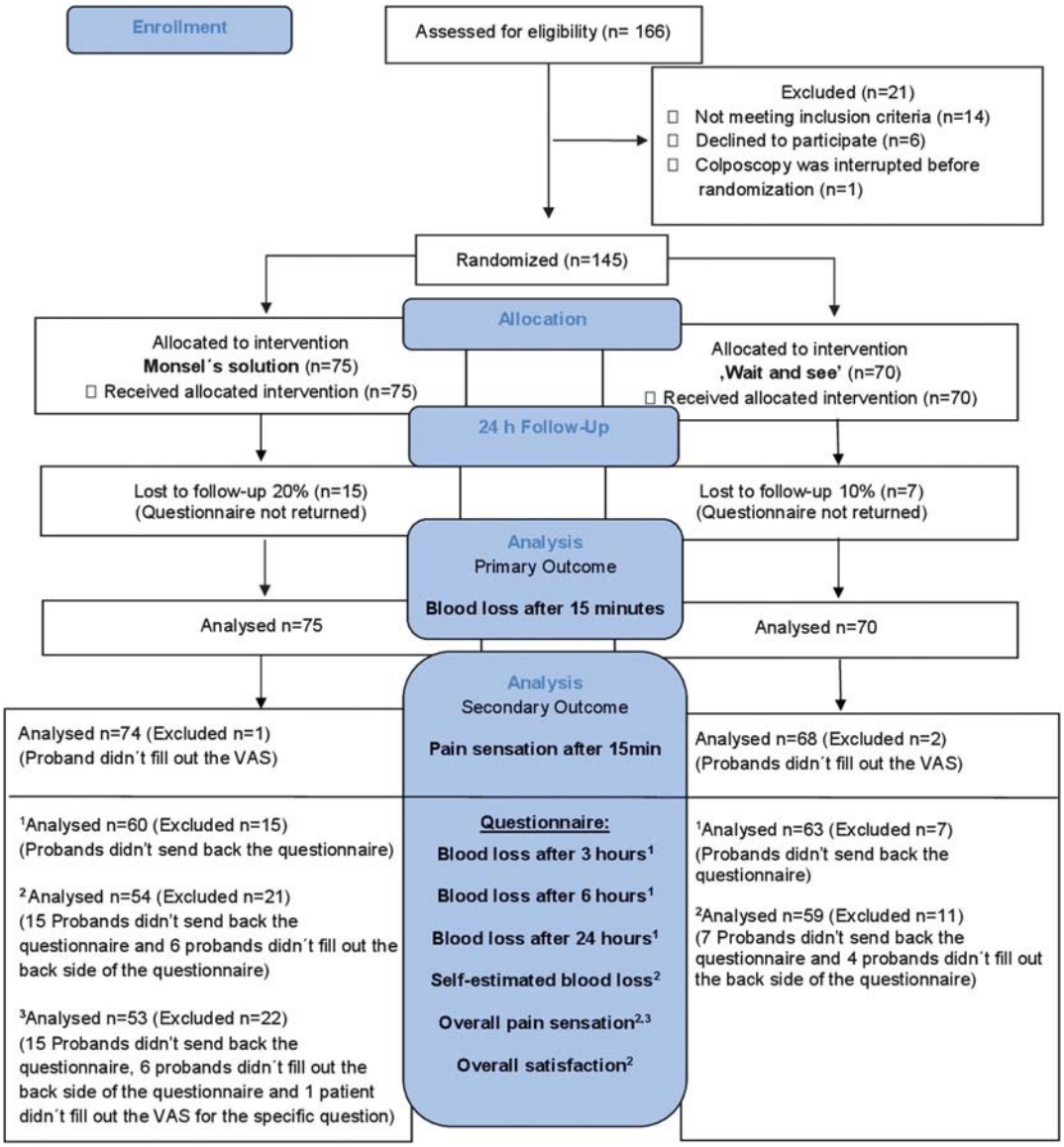

FIGURE 2. Consort diagram of the study probands' flow through the study. VAS indicates visual analog scale.

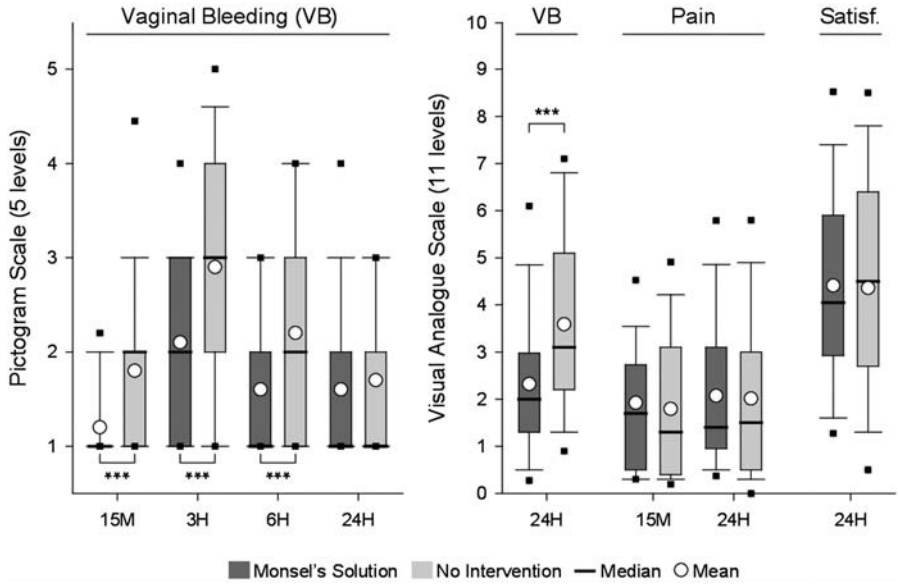

FIGURE 3. Amount of vaginal bleeding (VB), pain, and patient satisfaction (Satisf.) compared between patients treated with Monsel solution (dark gray) versus no intervention (light gray) after cervix sampling and measured at different time points after the procedure (15 minutes and 3, 6, and 24 hours) using a 5-level pictogram scale (lower values correspond to lower amount bleeding) or an 11-level visual analogue scale (lower values correspond to lower amounts of bleeding, pain, or satisfaction). Box plots: thick lines indicate medians, boundaries, and whiskers, and filled squares indicate the 25th/10th/5th, and the 75th/90th/95th percentiles, respectively. Open circles represent the means. Levels of significance are indicated (Mann-Whitney *U* test): ***$P \leq 0.001$.

Pain scores after 15 minutes and estimation of overall pain after 24 hours were not significantly different between the 2 study groups (19.2 ± 14.4 vs 17.9 ± 16.2, $P = 0.3$; and 20.7 ± 15.8 vs 20.1 ± 18.0, $P = 0.5$; respectively). Lastly, overall satisfaction also did not differ between groups (44.1 ± 21.5 vs 43.6 ± 23.2, $P = 0.9$).

There were 9 treatment associated complications. Specifically, 1 patient had a need for sutures because of severe bleeding 5 hours after CGCB. One patient lost her consciousness immediately after CGCB and recovered without further intervention. Both patients were in the control group ("wait and see"). The other 7 patients with complications were in the Monsel solution group. Specifically, 5 patients had an uncomfortable discharge 1 to 3 days after examination, 1 patient reported severe bleeding for more than 5 days but did not require further treatment, and 1 patient had severe vaginal bleeding 3 hours after CGCB requiring inpatient care. This patient received a vaginal packing without Monsel solution for 24 hours. The rate of complications was not significantly different between the 2 study groups (7/75 [9%] in the Monsel solution group vs 2/70 [3%] in the "wait and see" group; $P = 0.2$).

In a multivariate logistic model with VB after 15 minutes as the dependent variable and study group assignment, body mass index, age, procedure duration, biopsy volume, parity, type of transformation zone, and histology as the independent variables, only study group assignment ($P < 0.001$; odds ratio, 0.14; 95% confidence interval, 0.05–0.44) independently predicted VB after 15 minutes (see Table, Supplemental Digital Content 3, http://links.lww.com/LGT/A37, which presents the multivariate analyses). In the linear regression analysis, both study group assignment and higher body mass index were associated with higher blood loss (see Table, Supplemental Digital Content 3, http://links.lww.com/LGT/A37, which presents the multivariate analyses).

In addition, we looked at predictors of pain after 15 minutes. In this regard, we performed another multivariate analysis, demonstrating that age ($P = 0.03$; odds ratio, 0.35; 95% confidence interval, 0.13-0.92), but not study group assignment, body mass index, procedure duration, biopsy volume, parity, type of transformation zone, or histology, were significantly associated with pain scores after 15 minutes (see Table, Supplemental Digital Content 3, http://links.lww.com/LGT/A37, which presents the multivariate analyses), that is, older patients experienced less pain.

DISCUSSION

Our study shows that the application of Monsel solution significantly reduces bleeding after CGCB but does not affect overall pain or overall satisfaction of women undergoing this procedure. Application of Monsel solution resulted in less objective bleeding measured by a pictogram after 15 minutes, 3 hours, and 6 hours but not 24 hours. Also, the patients' subjective estimation of overall VB during 24 hours was lower after Monsel solution. However, pain scores after 15 minutes, overall pain estimation after 24 hours, and overall patient satisfaction were not significantly different between groups. Together, these data suggest that the application of Monsel solution after CGCB is effective in continuously reducing VB during the first 6 hours after the procedure. However, overall pain and satisfaction estimations are not improved by this intervention, indicating that the clinical benefit of Monsel solution is small.

Our study is the first head-to-head, randomized, comparative trial assessing the safety and efficacy of Monsel solution after CGCB. It is reasonable to use Monsel solution after CGCB because this intervention has been shown to be effective in women undergoing cervical conization. For example, a randomized trial found that packing with Monsel solution after cervical conization was equivalent to local electrocoagulation.[4] In accordance with this finding, Kietpeerakool et al determined the benefit of an immediate application of Monsel solution versus no application in 285 women with LEEP of the cervix.[9] They found that in the Monsel group, the duration of uncomplicated vaginal bleeding was significantly shorter and the occurrence of persistent vaginal

bleeding was significantly lower. The occurrence of severe complications that required treatment, including bleeding, was not significantly different between the 2 groups. However, the amount of surgical trauma is significantly greater during cervical conization than during CGCB. Therefore, extrapolation of study results collected in women undergoing conization to women undergoing CGCB is problematic. However, these data are consistent with our finding that Monsel solution significantly reduces short-term bleeding after cervical biopsies. Thus, the results of our study and the results of studies performed in women undergoing cervical conization confirm that the application of Monsel solution is an effective measure to reduce vaginal bleeding.

In our study, 5 (7%) of 75 patients who received Monsel solution experienced an uncomfortable discharge 1 to 3 days after examination. Because we did not observe this in the control group, prolonged discharge may be a specific side effect of Monsel solution. Moreover, because of the coagulation of blood, it can appear as "tissue." Thus, patients should be made aware of these side effects when undergoing the application of Monsel solution.

Although VB after 24 hours was equivalent in both treatment groups, Monsel solution did significantly reduce VB in the short term, that is, up to 6 hours after CGCB. Thus, it is reasonable to assess risk factors for VB after CGCB. In this way, women who might benefit most from Monsel solution may be identified. However, when we performed a multivariate analysis with VB after 15 minutes as the dependent variable, none of the investigated parameters was independently associated with it. Thus, neither parity nor age, biopsy volume, or type of the transformation zone is a reliable predictor of a greater likelihood to experience strong VB after CGCB. If a selective use of Monsel solution is intended, probably the best way to use this intervention is to restrict it to women who have a strong bleeding immediately after taking the biopsies.

Our study has limitations. First, patients in this trial were selected. For example, women with a history of conization and those with known or suspected coagulation disorders were excluded. Thus, the external validity of this study is limited to women comparable to the study population. Second, we cannot report adverse events after several days because the follow-up in our study was limited to 24 hours. Third, we have no long-term follow-up data and cannot rule out differences between the 2 study groups regarding late adverse events such as vaginal infections. Finally, this study does not exclude that other hemostatic interventions such as silver nitrate might be superior or inferior to the interventions tested in this trial. All of these limitations have to be acknowledged when interpreting the results of our study.

CONCLUSIONS

The application of Monsel solution significantly reduces bleeding for 6 hours after cervical biopsy but does not affect overall pain or overall satisfaction of women undergoing this procedure. Therefore, its use can be restricted to women who have a strong bleeding immediately after taking the biopsies.

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