International Journal of Obstetric Anesthesia (2019) 38, 19–24
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https://doi.org/10.1016/j.ijoa.2018.10.012

ORIGINAL ARTICLE

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Determination of ChloraPrep® drying time before neuraxial anesthesia in elective cesarean delivery. A prospective observational study

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ABSTRACT

Background: ChloraPrep® is a skin antiseptic commonly used before neuraxial anesthesia. It is believed that skin must be allowed to dry to prevent nerve damage by seeding ChloraPrep® solution into the neuraxis. We aimed to determine ChloraPrep® drying time in pregnant women before initiation of neuraxial anesthesia.

Methods: In 18 parturients undergoing elective cesarean delivery the skin 'wetness' after standardized ChloraPrep® application was prospectively assessed by blotting the skin with tissue paper and observing for residual orange tint. The isopropyl alcohol drying time was indirectly assessed by measuring the alcohol vapor concentration above the skin with a volatile organic compound analyzer. The primary outcome was the time measured from the end of skin preparation until tissue paper was no longer stained with orange tint. The secondary outcome was the time measured from the end of skin preparation until an abrupt reduction of isopropyl alcohol vapor concentration indicating that no further significant evaporation of alcohol was occurring.

Results: The mean ChloraPrep® drying time assessed by blotting the skin with tissue paper was 123 s (SD 32 s, 95% CI 107 to 140 s, range 85–195 s). The estimated isopropyl alcohol drying time was 82 s (95% CI 77.4 to 86.3 s).

Conclusion: Our results suggest that ChloraPrep® drying time may be longer than the current manufacturer-recommended guideline of three minutes. The amount of ChloraPrep® used, application methods, patient characteristics, and environmental factors could influence the drying time.

Keywords: ChloraPrep®; Chlorhexidine gluconate; Isopropyl alcohol; Drying time

Introduction

Chlorhexidine gluconate (CHG) is a skin antiseptic commonly used before neuraxial anesthesia. As part of routine clinical practice at BC Women's Hospital, we use ChloraPrep®OneStep (CareFusion Canada ULC, Dundas, ON, Canada) 10.5 mL applicators for skin antisepsis prior to neuraxial anesthesia. These applicators contain 2% CHG, 70% isopropyl alcohol (IPA), water, and an orange tint. Both CHG and IPA have been shown to be neurotoxic upon direct contact with nerve tissue, in both animal and in vitro studies.[1–3] A severe adhesive arachnoiditis with resultant paraplegia has been attributed to the accidental contact of CHG in alcohol with spinal[4] and epidural[5,6] nerve tissues in parturients. In an effort to decrease the risk of nerve damage by seeding the ChloraPrep® solution into deeper structures within the neuraxis, the antiseptic solution must be allowed to dry on the skin before needle puncture.[7]

ChloraPrep® drying times recommended by the manufacturer relate to skin antisepsis before surgical procedures, not before neuraxial anesthesia. Current guidelines including The Association of Anaesthetists 'Safety Guidelines: skin antisepsis before central neuraxial blockade'[7] do not specify how long to wait for the skin preparation solution to dry. To our knowledge

Accepted October 2018
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there are no studies in the literature investigating ChloraPrep® drying time before neuraxial anesthesia. Therefore, the primary aim of this study was to determine the length of time needed for the skin of the back to completely dry, after ChloraPrep® application in parturients scheduled for cesarean delivery (CD) under neuraxial anesthesia. The secondary aim was to measure the drying time of the IPA component of the ChloraPrep® in a more objective manner.

Methods

The design of this prospective observational study followed Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[8] The study was registered at ClinicalTrials.gov (NCT02095535). Data were collected between April 8 and May 8, 2014 at BC Women's Hospital (BCWH), University of British Columbia, Vancouver, Canada. After local ethics board approval (H14-00623), a signed informed consent was obtained from 20 healthy parturients, age $\geq$19 years, and gestational age $\geq$37 weeks, admitted for scheduled CD under neuraxial anesthesia. Exclusion criteria were: inability to communicate in English, active labor, body mass index (BMI) $\geq$35 kg/m^2, significant body hair over the intended application site, allergy to CHG or IPA, and contraindications to neuraxial anesthesia. The measurements took place in the operating rooms immediately before the scheduled surgery.

A trained investigator (AD) performed all skin blotting with a 3 $\times$ 5 cm piece of tissue paper (White Swan, Kruger Products L.P., Streetsville, ON, Canada). Another trained investigator (PS) performed all skin preparations and IPA vapor measurements. A calibrated ppbRAE 3000 (RAE Systems Inc., San Jose, CA, USA, serial number 594-901630) volatile organic compound analyzer was used to measure IPA vapor concentration.

Participants were seated upright on the operating table with their backs exposed, as per usual routine before neuraxial anesthesia. Investigators wore surgical masks and non-sterile gloves. Operating room staff movement near the participants was limited, to avoid any possible bulk air-flow interference with the ChloraPrep® drying and the IPA vapor concentration measurements. Prior to skin preparation a standardized area of skin was measured with a ruler, as a circle with a diameter of 20 cm and a center between the L2 and L3 (L2–3) lumbar vertebrae. The ambient air temperature was measured with a digital room thermometer WT137UCA (La Crosse Technology Ltd, Montreal, Quebec, Canada). Sublingual and skin temperatures were recorded using Filac 3000 AD (Covidien, Mansfield, MA, USA) and STS-400 (Smiths Medical, Dublin, OH, USA) thermometers, respectively.

Before the skin antiseptic application, the ppbRAE 3000 was turned on for 15 seconds to sample the background and to determine the baseline for the IPA measurements (Fig. 1). A pre-weighed ChloraPrep® applicator was then removed from its sterile package and the solution was applied in a circular motion with uniform pressure, starting from the center, and progressing peripherally clockwise to completely wet the skin area over five seconds. The ChloraPrep® was applied homogeneously to wet the area while avoiding the solution dripping down along the skin. The applicator was then placed back in its package, sealed in a plastic bag, and weighed to determine the amount of the antiseptic solution that had been applied to the skin.

The participant's skin was blotted with tissue paper every 15 seconds, commencing 30 seconds after ChloraPrep® application. The blotting was standardized as a brief light touch of the skin with an index finger covered with tissue paper, and without any rubbing motion. The skin was blotted starting at the 12 o'clock position and continued in a clockwise direction at the periphery of the preparation area (1 pm, 2 pm, 3 pm, etc.) until two consecutive blots showed no orange tint.

The IPA vapor concentration was continuously measured, starting immediately after the ChloraPrep® application. The analyzer sampling inlet was positioned above the center of the preparation area one cm from the skin. The standardized one cm distance of the analyzer inlet from the skin was assured by pre-attaching a plastic straw to the instrument sampling shaft, protruding exactly one cm, to touch the skin. The study ended four minutes after the vapor analyzer was turned on.

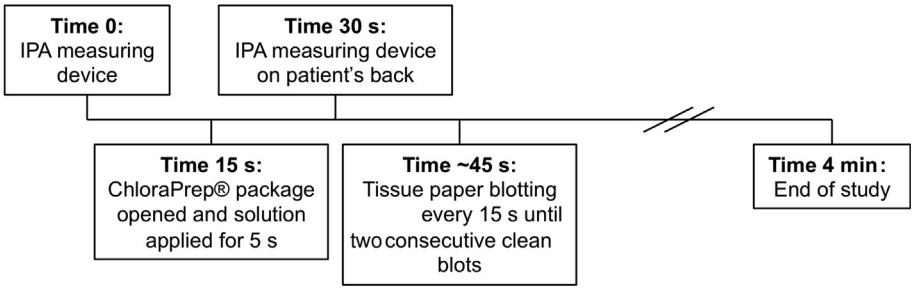

Fig. 1 Study timeline. IPA: isopropyl alcohol

Once data collection was finished, the patients were prepared again in the usual sterile fashion with a new ChloraPrep® applicator, by the attending anesthesiologist not involved in the study.

The ppbRAE data were downloaded from the instrument to a personal computer and later analyzed at the School of Population and Public Health, University of British Columbia (GA, MM, and VE).

ChloraPrep® drying time was measured from the end of the skin preparation to the point at which the second of two consecutive tissue papers, 15 seconds apart, were no longer stained with orange tint. Mean and standard deviation (SD) were used to calculate ChloraPrep® drying time.

The time from the end of the skin preparation to an abrupt reduction of IPA vapor concentration (indicating that no significant further evaporation was occurring) was considered the IPA drying time. A multiple breakpoint linear regression analysis, as implemented in the segmented package[9,10] in R[11] was used to determine the abrupt reduction of IPA vapor concentration.

Literature search showed no comparable study to assist with the sample size calculation. We arbitrarily chose to recruit 20 participants.

Results

Demographic data and clinical variables are presented in Table 1. The study procedure timeline is depicted in Fig. 1. Twenty parturients were recruited and 18 participants were analyzed. The first two participants were excluded because the start of the IPA vapor concentration measurement was delayed.

The mean ChloraPrep® drying time assessed by blotting the skin with tissue paper was 123 s (SD 32 s, 95% CI 107 to 140 s), and the range was 85 to 195 s (Fig. 2). Using the breakpoint regression analysis, the estimated mean IPA drying time measured by the ppbRAE analyzer was 82 s (95% CI 77.4 to 86.3 s). No adverse reactions were observed.

Table 1 Demographic data and clinical variables

Age (y)	35.4 ± (2.6)
Body mass index (kg/m^2)	29.7 ± (4.9)
Gestational age (weeks)	38.7 ± (0.8)
Parity	n [%]
0	7 [39]
1	8 [44]
2	3 [17]
Core temp (°C)	36.5 ± (0.3)
Skin temp (°C)	32.7 ± (0.7)
Room temp (°C)	23.6 ± (1.0)
Relative humidity (%)	33 ± (5)
ChloraPrep® pre-weight (g)	30.0 ± (0.3)
ChloraPrep® post-weight (g)	29.0 ± (0.3)

Data are mean ± (standard deviation) or number [percentage].

Discussion

Following standardized skin preparation with ChloraPrep®, we found that the skin of all participants was dry after three minutes and 15 seconds, when assessed by blotting the skin with tissue paper. We also determined that the upper limit of the 95% CI for the IPA drying time was 86 seconds, as indicated by low concentration levels of isopropyl alcohol vapor.

ChloraPrep® consists of 2% CHG w/v (weight/volume percentage concentration, that is 2 g of CHG per 100 mL of solution), 70% IPA v/v (volume/volume percentage concentration, that is 70 mL of IPA per 100 mL of solution), purified water, and an orange tint (FD&C yellow #6). Chlorhexidine gluconate is the chief antimicrobial agent and the orange tint allows for visual demarcation of the skin preparation area. Isopropyl alcohol potentiates the antimicrobial effect of CHG and speeds up the onset time. The evaporation rate of IPA, compared to water, is significantly faster. Therefore, it was not surprising to observe that the measured IPA drying time was shorter (by about 45%) than the total ChloraPrep® drying time. Nevertheless, our results support waiting at least three minutes and 15 seconds after ChloraPrep® application to ensure a patient's skin is completely dry before performing neuraxial anesthesia.

For skin preparation prior to surgery, the manufacturer of ChloraPrep® advises: "Allow the solution to completely dry for a minimum of three minutes on hairless skin; up to one hour in hair; do not blot or wipe out."[12] However, the print on the sterile packaging of individual ChloraPrep® applicators states: 'allow area to dry completely; approximately 30 seconds'. In addition, the manufacturer advises: "Do not use for lumbar puncture or in contact with the meninges."[12] The Royal College of Anaesthetists, the American Society of Anesthesiologists, and the American Society of Regional Anesthesia, all endorse the use of CHG as the skin antiseptic of choice before neuraxial anesthesia.[13–15] However, none of these regulatory bodies, nor the most recent clinical practice guideline 'Safety Guidelines: skin antisepsis before central neuraxial blockade'[7] specify a waiting time after CHG skin application or how to assess skin wetness or dryness. The blot test that we utilized in our study is not meant as a suggested technique for use in clinical practice. It was merely a simple method to ascertain when the ChloraPrep® solution was dry to touch in this research setting. In emergency CD, a conflict may arise between proceeding rapidly with neuraxial anesthesia to expedite delivery and waiting sufficiently long to allow ChloraPrep® to adequately dry.

The neurotoxicity of CHG has been well documented in both animal models and in vitro studies. As early as 1955, Hurst[1] reported that CHG was neurotoxic when

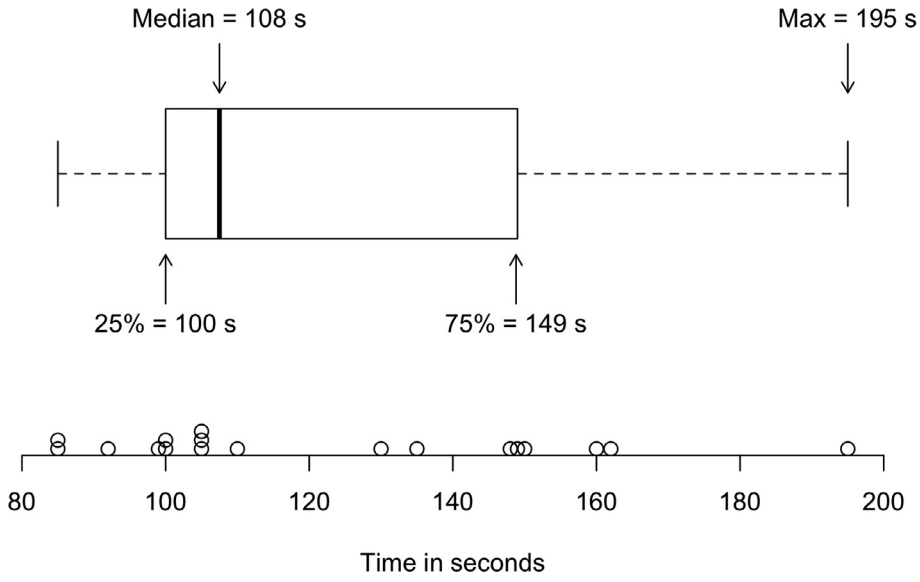

Fig. 2 ChloraPrep® drying time. Open circles represent drying times for individual participants

administered intrathecally in monkeys. In another animal study published in 1984, Henschen and Olson[2] demonstrated a CHG-induced degeneration of adrenergic nerves in rat eyes. Doan et al.[3] studied the in vitro cytotoxicity of CHG with nine serial dilutions of CHG, from 2% to 0.01%, in human neuroblastoma cells and rat Schwann cells. A colorimetric assay was used to evaluate cell viability. Chlorhexidine gluconate in all concentrations significantly decreased the viability of both cell types after a 10-minute exposure.

In humans, the neurotoxicity of CHG has been implicated as a cause of devastating neurological complications, including adhesive arachnoiditis and paraplegia. In 2012, Bogod summarized several catastrophic cases that had occurred in general surgical, orthopedic and obstetric patients.[5] Although a direct association between CHG and nerve damage in these cases was never scientifically proven, it seemed likely that some of these cases had arisen from accidental contamination of needles or syringes with 'splashes' of antiseptic during neuraxial blockade. The conclusion of this editorial emphasized meticulous attention to detail while performing neuraxial blockade and working with highly toxic substances that could come to lie in close proximity to vulnerable nerve tissue. In another editorial, Checketts advised taking great care to avoid accidental splashing of spinal needles, syringes or catheters with cleaning solution when performing central neuraxial blockade.[16]

We acknowledge several limitations of our study. Lacking any previously published data for a power calculation, we recruited only a small number of participants to perform a pilot study. A larger sample size could possibly provide more accurate results with more precise confidence intervals.

When this study was designed and conducted, we were not aware of any standardized and validated instrument that could be used to assess skin wetness in vivo. Therefore, we chose to measure the ChloraPrep® drying time based on subjective observations of the orange tint on tissue paper. To minimize the inter-rater variability, we employed only one person to assess the orange tint staining in all participants. We now understand that two-point moisture meters (protimeters), used in environmental applications, may possibly provide more objective measurements of moisture levels at the skin compared to blotting. The IPA drying time was assessed indirectly by measuring IPA vapor concentration over the skin preparation area with a ppbRAE 3000 analyzer. This handheld analyzer (RAE Systems, Sunnyvale, CA, USA) is widely used in industrial hygiene and military applications and can be selectively calibrated to measure solvent vapor at concentrations as low as five parts per billion (ppb). The sampling flow rate of the analyzer suction pump is 500 mL per minute, and the sensor features a three-second response time. Therefore, the analyzer can quickly detect an abrupt decline of vapor concentration that corresponds to the cessation of IPA evaporation from the skin surface.

We recognize that the manufacturer of ChloraPrep® recommends applying the solution for surgical preparation in horizontal strokes and for at least 30 seconds. We standardized the skin preparation to a circular area of 20 cm diameter around the proposed needle insertion site and applied ChloraPrep® lightly, just to wet the skin while avoiding the solution running across the skin. We chose this standardized skin preparation method because we believed that letting the antiseptic run on the skin and to soak the operating table sheet under the participants could falsely prolong the IPA drying time measurement with the volatile compound analyzer. Some anesthesiologists may prefer painting a much larger window and applying the antiseptic

more heavily and repeatedly. Therefore, the drying time may be different in such circumstances.

We also acknowledge that 0.5% rather than 2% CHG is commonly used in many United Kingdom and European hospitals. Although The Association of Anaesthetisits of Great Britain and Ireland currently recommend a 0.5% solution,[7] many anesthesiologists and institutions use a 2% solution of CHG.[17,18] Indeed, 2% CHG in 70% IPA is the only available chlorhexidine concentration at our institution.

We did not attempt to quantify the CHG and IPA skin residue after the superficial skin drying, and we also excluded high BMI patients from recruitment, since the skin preparation solution may pool in skin folds and take a longer time to dry. Whether any residual CHG can be transferred from the dried skin to surgical gloves and subsequently to instruments needs to be determined. It is also possible that some potentially neurotoxic matter is absorbed more deeply into the stratum corneum and that even though the surface of the skin appears to be dry, this 'hidden' matter may still be a source of seeding with the neuraxial needle. Furthermore, the potential for neurotoxicity from the orange tint has not been proposed, but should be considered and investigated. Finally, it is a routine practice at our institution to only apply a single coat of ChloraPrep®. Therefore, we did not attempt to compare the drying times after one versus two applications. Malhotra et al. demonstrated that a second application of 0.5% CHG spray for disinfecting the skin in 309 volunteers did not provide any benefit, as assessed by counting colony-forming units on agar plates that were applied to the skin after the antiseptic sprays.[19] However, some practitioners may still choose to use two CHG applications. A second application of antiseptic could increase the drying time, as the evaporation of IPA in ChloraPrep® is an endothermic process, and thus may cool the skin surface.

In conclusion, despite widespread use of ChloraPrep®, a knowledge gap exists regarding its skin drying time in pregnant women scheduled for CD under neuraxial anesthesia. Our data suggest that the drying time may be longer than the currently recommended three minutes. Further studies are required to evaluate the ChloraPrep® drying time in a larger sample size, with different CHG concentrations and application amounts, perhaps using more objective methods to assess the skin dryness; and by different operators, in laboring parturients, and in non-obstetric patients.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of interest

None.

Acknowledgements

We thank Marcia Moulton from Concept Controls, Burnaby, Canada for renting us the ppbRAE 3000 equipment. Also, we thank Victoria Euper, BSc, for help with data analysis. Dr. Astrakianakis' appointment was funded in part by the Michael Smith Foundation for Health Research – Scholar Award program.

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