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The Importance of Isopropyl Alcohol in Skin Preparation Solutions

To the Editor—We read with great interest the recent article by Lee et al[1] comparing chlorhexidine and iodine for skin antisepsis to prevent surgical site infection. We wish to commend the authors for their timely execution and thoughtful approach to this analysis.

We would like to contribute to this discussion by pointing out what we believe to be a very important aspect of the debate: the importance of isopropyl alcohol in solutions. Isopropyl alcohol (IPA) has been shown in both in vitro and in vivo studies to be a powerful and rapid antiseptic agent on the skin. According to many studies and texts on the subject, both chlorhexidine and iodine have an intermediate onset of action and a later peak effect, thus making the combination of immediate action provided by IPA and delayed action in the mixed solutions theoretically superior to chlorhexidine and iodine alone. In their meta-analysis, the authors made no distinction between solutions containing IPA and those that did not contain this important agent when they drew the conclusion that chlorhexidine is superior to iodophores. We present an argument against this conclusion.

First we would like to discuss a large prospective study by our group that compared surgical site infection (SSI) rates during 3 separate 6-month time periods (spanning from January 1, 2006, to June 30, 2007) during which 3 different skin preparation protocols employing IPA were used for all adult general surgery cases at our institution.[2] We found that rates of SSIs were significantly decreased when iodophore-based skin preparation solutions containing IPA were used, compared with SSI rates when solutions of chlorhexidine plus IPA were used. Because all preparation protocols included IPA, we could isolate the nonalcohol component (chlorhexidine, iodine-providone, and iodine povacrylex were used in our study), and we concluded that iodine-based solutions were most likely superior to chlorhexidine-based solutions in both intention-to-treat and per-protocol models.

Furthermore, when examining the studies used in the systematic review by Lee et al,[1] we see that the authors found only 3 studies (Saltzman et al,[3] Ostrander et al,[4] and Veiga et al[5]) that compared iodophore solutions that contain alcohol with chlorhexidine solutions that contain alcohol. In these studies, the outcomes measured were positive skin swab cultures and/or SSIs. In the Saltzman et al[3] and Ostrander et al[4] studies, there were fewer positive skin swab cultures in the chlorhexidine group, but the SSI rates were not significantly different between the two groups. Only in the study by Veiga et al[5] were they able to show a decrease in SSI rates in the chlorhexidine group. With the exception of the studies by Culligan et al[6] (which compared 2 non–IPA-containing solutions) and Berry et al[5] (which contained a chlorhexidine-plus-spirits solution), all of the other studies compared chlorhexidine plus IPA with iodophore agents that did not contain alcohol. We do not believe that this is a valid comparison.

The alcohol component in skin preparation solutions is important. We do not agree with Lee et al's[1] conclusion from their systematic review that chlorhexidine is superior to iodine in the prevention of surgical site infections.

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Reply to Maiwald et al and Riccio et al

To the Editor—We thank Maiwald et al[1] and Riccio et al[2] for their interest in our meta-analysis, which reported a decreased number of surgical site infections (SSIs) in patients who underwent preoperative skin antisepsis with chlorhexidine-based formulations, compared with patients treated with iodine-based formulations.[3] The authors raise an interesting point, suggesting that the effectiveness of chlorhexidine-based formulations may be attributable to alcohol rather than to chlorhexidine. They include the following points in support of their hypothesis, which we appreciate having the opportunity to address below.

First, they state that alcohol is the primary active ingredient in chlorhexidine-alcohol and iodine-alcohol formulations, and that formulations with alcohol are better antiseptics than aqueous formulations. We identified a Cochrane review that summarizes the results from several randomized controlled trials (RCTs) evaluating the efficacy of preoperative skin antiseptics including non–chlorhexidine-based solutions.[4] The meta-analysis reported no significant difference between iodine-alcohol and aqueous iodine in decreasing SSI rates.[4] Additionally, the meta-analysis included the study by Berry et al[5] that found that chlorhexidine 0.5% in alcohol was more effective than povidone-iodine 10% in alcohol in preventing SSIs. In summary, the results from these studies conflict with the hypothesis that alcohol is the primary active agent in antiseptic formulations with alcohol.

Second, they referenced a study by Swenson et al,[6] which compared 3 skin preparations sequentially over 6-month periods (period 1, povidone-iodine scrub-paint with isopropyl alcohol [IPA] between steps; period 2, 2% chlorhexidine and 70% IPA; and period 3, iodine povacrylex in IPA). The authors report that iodophor-IPA formulations were associated with fewer SSIs than were chlorhexidine-IPA formulations.[6] The results are intriguing, but the conclusions need to be tempered, given the inherent limitations of quasi-experimental studies, particularly the lack of random assignment and the difficulty in ascertaining whether statistical significance is due to causal association or an alternative explanation (ie, regression to the mean, maturation effects, and/or inadequate control of important confounders).[7] For this reason, our meta-analysis was limited to RCTs and, therefore, did not include Swenson et al.[6]

Third, they state that there is significant heterogeneity in the antiseptic formulations, surgeries, and outcomes in the RCTs included in our meta-analysis. To clarify, the purpose of our meta-analysis was to compare the efficacy of chlorhexidine-based formulations with that of iodine-based formulations in decreasing the primary outcome of interest, SSI, and the secondary outcome of interest, positive skin culture results after antisepsis. The formulations used in these studies, including the concentrations and whether or not they included alcohol, were listed in Table 1 in our article.[3] We included all surgical interventions because inadequate disinfection of the operative site can result in SSI regardless of the type of surgery. The primary and secondary outcomes were then analyzed and presented separately, and the tests for heterogeneity were nonsignificant ($I^2 = 0\%$ for both analyses).[3] To address the concerns of Riccio et al[2] and Maiwald et al,[1] we performed the following subanalyses, directly