The Significance of Elevated Levels of Parathyroid Hormone in Patients With Morbid Obesity Before and After Bariatric Surgery

Nahid Hamoui, MD; Kiwan Kim, BS; Gary Anthone, MD; Peter F. Crookes, MD

Hypothesis: The risk of hyperparathyroidism after the duodenal switch operation is related to the length of the common channel.

Design: A retrospective analysis of patients following the duodenal switch operation from October 2, 2000, through February 1, 2002.

Setting: Academic tertiary referral hospital.

Patients: One hundred sixty-five consecutive patients underwent the duodenal switch operation, performed for morbid obesity, with common channel lengths of 75 cm (n=103 [group A]) and 100 cm (n=62 [group B]).

Main Outcome Measures: Weight loss and parathyroid hormone, corrected calcium, and 25-hydroxyvitamin D (25-OH D) levels were compared between groups A and B. Values were determined preoperatively, early postoperatively (3-6 months), and late postoperatively (9-18 months).

Results: Both groups exhibited a slight reduction in serum calcium concentration, with one quarter decreasing below the normal range. Hyperparathyroidism was more common in group A than group B preoperatively (38.9% vs 14.9%), reflecting the higher body mass index of patients in group A. Hyperparathyroidism was also more frequent in the early (54.9% vs 30.9%) and late (49.4% vs 20.5%) postoperative periods in group A vs group B. New-onset hyperparathyroidism was also more common in group A than group B (42.0% vs 13.3%). After 1 year, subnormal 25-OH D levels were found in 17.0% of the patients in group A and in 10.0% of the patients in group B. Median 25-OH D levels increased in both groups, but tended to be higher in group B.

Conclusions: Patients with shorter common channels had a higher risk of developing hyperparathyroidism. This may be related to limited 25-OH D absorption.

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Bariatric surgery produces weight loss by either restriction of intake or malabsorption. The greatest weight loss is achieved by primarily malabsorptive procedures. The benefits of weight loss from these procedures must be balanced against the risk of producing nutritional deficiencies, such as anemia, hypocalcemia, and protein-calorie malnutrition.

The duodenal switch operation combines a restrictive and a malabsorptive component. Restriction is produced by the linear sleeve gastrectomy, preserving the pylorus, and some degree of malabsorption is created by biliopancreatic diversion (BPD), with absorption of fats being restricted to the portion of the terminal ileum distal to the junction of the alimentary and biliopancreatic limbs, termed the common channel. This is generally made 50 to 100 cm long (Figure 1).

Reduced calcium absorption after this procedure is thought to be caused by 2 mechanisms: (1) ingested food bypasses the duodenum and proximal jejunum, where calcium is maximally absorbed; and (2) there is defective absorption of fatsoluble vitamins, including vitamin D, which promotes calcium absorption. This relative lack of calcium stimulates the production of parathyroid hormone (PTH). The action of PTH is to cause increased production of 1,25-dihydroxyvitamin D and increased reabsorption of calcium from bone. This physiologic compensatory process, therefore, maintains a normal serum calcium level at the expense of bone loss. The long-term risk of osteoporosis is of particular concern in the bariatric population, because most are middle-aged women already at risk for bone loss later in life.

There are few detailed studies of calcium and bone metabolism after bariatric surgery...
We had the opportunity to study calcium metabolism in 2 different forms of the duodenal switch operation, with common channels of 75 or 100 cm. The aim of this study was to determine if the longer common channel resulted in fewer abnormalities in calcium metabolism after the duodenal switch operation.

METHODS

SUBJECTS

The study population consisted of 165 consecutive patients who underwent the duodenal switch operation from October 2, 2000, to February 1, 2002. During this period, there was a gradual transition from performing the procedure with 75-cm common channels to constructing 100-cm common channels. We studied both groups of patients: 103 patients with a common channel of 75 cm (group A) and 62 patients with a common channel of 100 cm (group B). The demographic data of the study population are as follows. The mean (range) age of patients in group A was 40.5 (18-61) years; in group B, 40.0 (20-64) years. There were 86 women and 17 men in group A, and 50 women and 12 men in group B. The differences in age (P = .63) and sex (P = .64) were not significant. The mean body mass index (BMI; calculated as weight in kilograms divided by the square of height in meters) in group A vs group B was 55.0 vs 47.5 (P < .001).

PROCEDURES

Total plasma calcium, PTH, and albumin levels and weight were measured preoperatively and postoperatively at 3-month intervals. Calcium levels were corrected for albumin by subtracting the albumin level from 4.0, multiplying the difference by 0.8, and then adding this to the calcium level. The 25-OH D level was measured preoperatively and at 12 and 18 months postoperatively. All patients were treated with a prenatal vitamin containing 400 IU of cholecalciferol beginning 2 weeks postoperatively. They also received 400 IU of cholecalciferol, 10000 IU of beta carotene (Allergy A and D), and 1000 to 1500 mg of calcium carbonate or calcium citrate containing 400 to 800 IU of cholecalciferol beginning at 6 to 10 weeks postoperatively. Patients with abnormal levels of calcium, PTH, or alkaline phosphatase had the doses of beta carotene and cholecalciferol increased to a maximum of 3 tablets a day.

DATA ANALYSIS

Median values for all outcome measures were compared between groups A and B using the Mann-Whitney test. The prevalences of patients having abnormal values were also calculated and were compared using the chi² test. The effect of aggressive supplementation was assessed by comparing the PTH, 25-OH D, corrected calcium, and alkaline phosphatase levels after standard vitamin supplementation with the levels after doubling the doses of beta carotene and cholecalciferol. Alkaline phosphatase values in patients with abnormal levels of other liver function test values (total bilirubin, aspartate aminotransferase, and alanine aminotransferase) were not included in this analysis. Comparisons were made using a matched nonparametric test. The Statistical Product and Service Solutions program (SPSS Inc, Chicago, Ill) was used for statistical analysis.

RESULTS

Median values for each 3-month interval of the follow-up period for PTH, 25-OH D, and corrected cal-
Cacium are presented in Figures 2, 3, and 4, respectively. The PTH level increased slightly over time. Patients with 75-cm common channels had a higher PTH level than those with 100-cm common channels preoperatively, and continued to do so until 18 months postoperatively, when the levels became similar (Figure 2). The prevalence of elevated levels of PTH was higher at all time periods in group A than group B (Table 1). New-onset hyperparathyroidism (the development of an elevated PTH level postoperatively when it was normal before surgery) occurred in 42.0% of group A and 13.3% of group B between 9 and 18 months (P = .02). (During the first 6 months, the values were 48.3% in group A and 28.9% in group B [P = .11].)

The prevalence of low 25-OH D levels was similar between groups A and B preoperatively (24.6% vs 19.4%; P = .56). The levels of 25-OH D increased in both patient groups during 1 year of follow-up; at 18 months, patients with 100-cm common channels had a higher level than patients with 75-cm common channels (Figure 3). Subnormal 25-OH D levels occurred in 17.0% of group A, but only in 10.0% of group B, between 9 and 18 months of follow-up (P = .46). (P = .32 for group A and P = .36 for group B when comparing the preoperative value with the value between 9 and 18 months.)

Groups A and B had a slight decline in calcium levels over time, although the median level remained within normal limits (Figure 4); calcium levels decreased below the normal range in one quarter of the patients between 9 and 18 months postoperatively in both groups (Table 2). Of the 165 patients, 51 (30.9%) were prescribed additional cholecalciferol supplementation during the follow-up period for laboratory abnormalities. This was more common in group A than group B (40.0% vs 24.2%);

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Table 1. Prevalence of Hyperparathyroidism*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Preoperatively</th>
<th>Postoperatively</th>
<th>P Value‡</th>
<th>Early</th>
<th>Late</th>
</tr>
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<tbody>
<tr>
<td>Common channel length, cm</td>
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<td></td>
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<tr>
<td>75</td>
<td>38.9</td>
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<td>.006</td>
<td>.002</td>
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</table>

Abbreviation: NA, data not applicable.
*Data are given as percentage of patients unless otherwise indicated.
‡Preoperative vs late postoperative.

Table 2. Prevalence of Hypocalcemia*

<table>
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<tr>
<th>Variable</th>
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<th>Postoperatively</th>
<th>P Value‡</th>
<th>Early</th>
<th>Late</th>
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<tbody>
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<td>Common channel length, cm</td>
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<td></td>
<td></td>
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</tr>
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<td>.82</td>
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</tbody>
</table>

Abbreviation: NA, data not applicable.
*Data are given as percentage of patients unless otherwise indicated.
‡Early indicates within the first 6 months; late, between 9 and 18 months.
§Preoperative vs late postoperative.
No significant changes were observed in PTH, 25-OH D, corrected calcium, or alkaline phosphatase levels after instituting the supplementation (Table 3).

Parathyroid hormone levels correlated positively with BMI preoperatively ($r = 0.31, P = .002$) and at 1 year ($r = 0.32, P = .006$). Patients with 75-cm common channels had a higher BMI preoperatively than those with 100-cm common channels. They lost more absolute weight postoperatively and lost a little less percentage of excess body weight than the patients with 100-cm common channels (Figure 5 and Figure 6). When all patients were divided into quartiles based on BMI, patients with higher BMI values lost more weight and less percentage of excess body weight than those with lower BMI values, and patients with 75- and 100-cm common channels had similar values in all quartiles (Figure 7 and Figure 8).

Patients with an increase in PTH level at 1 year postoperatively lost less weight than those who had a decrease in PTH level (58.95 vs 62.55 kg; $P = .02$). Patients who had elevated PTH levels at 1 year postoperatively had a higher preoperative BMI than those with normal PTH levels (58 vs 52; $P = .007$). The PTH levels at 1 year correlated positively with preoperative PTH levels ($r = 0.62, P < .001$). The PTH levels at 1 year postoperatively did not correlate with corrected calcium, alkaline phosphatase, or 25-OH D levels. Although the expected inverse relationship between 25-OH D and PTH levels did not reach statistical significance at 1 year postoperatively ($r = -0.25, P = .06$), patients with a 25-OH D level of less than 20 ng/mL did have a higher PTH level at 1 year than those with a 25-OH D level of 20 ng/mL or higher (61 vs 49 pg/mL [6.4 vs 5.2 pmol/L]; $P = .009$). Similarly, corrected calcium levels did not correlate with ei-

### Table 3. Median Laboratory Values Before and After Treatment With Beta Carotene and Cholecalciferol

<table>
<thead>
<tr>
<th>Variable</th>
<th>Before Treatment</th>
<th>After Treatment</th>
<th>$P$ Value</th>
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<tbody>
<tr>
<td>PTH level, pg/mL</td>
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<tr>
<td>Corrected calcium level, mg/dL</td>
<td>9.0</td>
<td>8.9</td>
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<tr>
<td>Alkaline phosphatase level, IU/L</td>
<td>88.0</td>
<td>82.0</td>
<td>.06</td>
</tr>
<tr>
<td>25-OH D level, ng/mL</td>
<td>17.9</td>
<td>15.0</td>
<td>.70</td>
</tr>
</tbody>
</table>

Abbreviations: 25-OH D, 25-hydroxyvitamin D; PTH, parathyroid hormone. SI conversion factors: To convert calcium to millimoles per liter, multiply by 0.25; to convert PTH to picomoles per liter, multiply by 0.1053.

* The dose of beta carotene and cholecalciferol (Allergy A and D) was increased from once to twice daily.

Figure 5. Median absolute weight lost. Error bars show interquartile range. The asterisk indicates $P = .001$; dagger, $P = .02$; and double dagger, $P < .001$. Groups A and B are defined in the legend to Figure 2.

Figure 6. Median percentage excess body weight loss (EBWL). Error bars show interquartile range. The asterisk indicates $P = .05$; dagger, $P = .001$; and double dagger, $P < .001$. Groups A and B are defined in the legend to Figure 2.

Figure 7. Median weight lost by body mass index (BMI) (calculated as weight in kilograms divided by the square of height in meters) quartile. Quartile 1 indicates a BMI of 38 to 50; 2, a BMI of 51 to 55; 3, a BMI of 56 to 61; and 4, a BMI of 62 to 61. Groups A and B are defined in the legend to Figure 2.

Figure 8. Median percentage excess body weight loss (EBWL) by body mass index (BMI) quartile. Groups A and B are defined in the legend to Figure 2, and BMI and the BMI quartiles are defined in the legend to Figure 7.

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The principal finding of this study is that PTH levels increased after the duodenal switch operation, especially in patients with a shorter common channel. It would be expected that PTH levels would decrease, because weight loss produced by dietary means causes reduction of PTH levels in those with morbid obesity. The postoperative elevation of PTH levels is in striking contrast to this expectation.

The significance of this observation must be interpreted in light of the preexisting abnormalities of PTH level in obese patients. The PTH levels have been found in small studies to be positively correlated with body weight. The present study of a much larger patient population is in agreement with these findings. One potential weakness of this study is that the selection of common channel length was not random; there was a tendency to select a shorter common channel for heavier patients. The 75-cm common channel group was, thus, heavier and had a higher baseline PTH level than the group with a 100-cm common channel. Nevertheless, in those patients whose baseline PTH levels were normal, the development of an elevated PTH level was more common in the 75-cm channel group. This clearly indicates the malabsorptive effect of the shorter common channel length.

There are several indications from our data that a difference of 25 cm of common channel length may cause a significant elevation of PTH level postoperatively. Patients with 75-cm common channels tended to have lower levels of 25-OH D than those with 100-cm common channels, reflecting the decreased absorption of vitamin D. We further found that low levels of 25-OH D were associated with higher levels of PTH, suggesting that the elevated PTH level occurred in response to reduced calcium absorption.

Both patient groups had an increase in median 25-OH D level postoperatively, although this increase was more marked in patients with 100-cm common channels. This is in contrast to the study by Marceau et al that showed that the vitamin D level decreased after a biliopancreatic bypass; however, most of the patients in this study had 50-cm common channels, who most likely had even greater impairment of vitamin D absorption than patients in this study. In addition, our patients received large amounts of exogenous vitamin D (cholecalciferol), which may have partially compensated for the decreased absorption of the vitamin.

Median levels of calcium decreased postoperatively, with about one quarter of patients in groups A and B becoming hypocalcemic in the late period. Calcium is absorbed preferentially in the duodenum; this process is facilitated by vitamin D. Although patients with low calcium levels also tended to have lower levels of 25-OH D, this relationship was not statistically significant and suggests that decreased calcium absorption by surgical exclusion of the duodenum is more important than reduced vitamin D levels.

Increasing the dose of cholecalciferol produced no appreciable change in PTH, 25-OH D, corrected calcium, or alkaline phosphatase levels. This does not imply that cholecalciferol supplementation has no beneficial effect on calcium metabolism because all our patients received some exogenous cholecalciferol. However, it does suggest that beyond a certain threshold, increasing the dose of cholecalciferol will not correct postoperative derangements in calcium metabolism.

None of the patients in this study had any clinical signs of hypocalcemia or bone disease. Measurements of urinary calcium level or markers of bone turnover were not performed, but are clearly important areas for future investigation. The degree of hypocalcemia that was observed was mild. It is not to be expected that serious clinical problems would emerge at this relatively early stage in the postoperative course. The importance of the biochemical abnormalities that we have reported lies in their potential to be harbingers of bone loss in the future. Evidence is emerging that operations producing significant malabsorption, such as BPD, may be associated with diminished bone density and an elevated PTH level, although the magnitude of these changes is disputed. Thus, the postoperative elevation of PTH levels may be an early signal of bone disease in some patients. Identifying these patients is especially important in the bariatric population, which has a high proportion of women at risk for bone loss later in life. In view of the fact that weight loss is similar between these 2 groups, there seems to be little justification for constructing the shorter common channel length, and we have abandoned it in our practice. Based on these early data, it seems that accuracy of common channel measurement may be critical in performing bariatric procedures involving some degree of malabsorption, and that the addition of as little as 25 cm of common channel may help minimize postoperative metabolic abnormalities after the duodenal switch operation. In light of the recent tendency to perform the duodenal switch laparoscopically, when measurement of bowel length is more cumbersome, ensuring accurate measurement of the common channel is especially important.

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This study was presented at the 74th Annual Meeting of the Pacific Coast Surgical Association; February 16, 2003; Monterey, Calif; and is published after peer review and revision. The discussions that follow are based on the originally submitted manuscript and not the revised manuscript.

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REFERENCES


Stanley R. Klein, MD, Torrance, Calif: Surgery for morbid obesity was introduced approximately 50 years ago, in part by a member of this organization. The life-altering and profound consequences of bariatric surgery have been recognized for 3 decades as the field emerged. The remarkable benefits were not well documented and appreciated until the last decade, following the publication of the 1985 and 1992 National Institutes of Health consensus statements on the health implications of obesity and appropriate indications for bariatric surgery. The prevalence of obesity and, specifically, morbid obesity should be fully appreciated by this audience. Disdain for the obese remains to be defined for a condition likely due to an inborn error of metabolism. In closing, I have several questions for the authors. (1) Do you have any information on the serum magnesium or bone density, the former of which, namely, the magnesium level, does influence parathormone function? (2) Has any patient presented to date with refractory secondary hyperparathyroidism? (3) Are these patients at risk for oxalate nephrolithiasis, a malady we all have become familiar with?

Bruce M. Wolfe, MD, Sacramento, Calif: The malabsorption of ingested fat is necessarily associated with increased calcium excretion in the feces due to calcium-free fatty acid complexing. My questions are: Do all patients with hyperparathyroidism necessarily have ongoing negative calcium balance, that is, chronic depletion of bony calcium? Second, is the development or detection of hyperparathyroidism in these patients sufficiently sensitive to detect all of the patients who in fact have a subtle but ongoing and, therefore, cumulative depletion of bony calcium? Third, could you say more about whether you routinely recommend calcium and vitamin D supplementation and do you have any data on whether compliance with the recommendations for not only calcium and vitamin D supplementation but also compliance with follow-up visits has an impact on outcome with regard to calcium metabolism?

Clifford W. Deveney, MD, Portland, Ore: One question pertains to the bone density studies because this is the major thing that we worry about in these patients. You had an earlier group that is several years out, more than 5 years, with a 30-cm common channel, several of which had hypocalcemia. Have you done any bone density studies on those patients, and have any of those patients developed osteoporosis?

Dr Crookes: May I just make a very brief comment about the reason we did this study? The duodenal switch operation is not mainstream, at least not yet, and it is frequently denied by insurance payers on the grounds that it creates malabsorption. They refuse to pay for it. So we had been trying to study it and to identify exactly what problems are actually produced by the malabsorptive component. We had this opportunity to compare 2 different constructions of the duodenal switch. The second thing that emerged was that even that 25 cm in the common channel appeared to make a difference. Those of you who are thinking of doing this operation laparoscopically will know how difficult it is to measure the length of intestine with that degree of precision. Twenty-five centimeters does appear to make a difference.

Having said that, I would like to provide the major answers to Dr Klein’s questions. He asked about magnesium. I presented. Of note was the fact that 51 (31%) of the 165 patients were prescribed additional vitamin D during the study, but this had little impact on the measured variables.

The statistical methods used by the authors are appropriate in comparing the 2 groups of patients. The data supporting their thesis include: (1) patients with a 75-cm common channel who had “normal” PTH levels preoperatively had a higher prevalence of postoperative HPT [hyperparathyroidism] than patients with 100-cm common channels despite losing more weight; and (2) patients with 75-cm common channels tended to have lower levels of 25-hydroxycholecalciferol than those with 100-cm common channels, reflecting a decreased absorption of the fat-soluble vitamin despite exogenous feeding in one third of the patients.

In summary, the authors have presented convincing data to support their thesis that, following a duodenal switch operation in the morbidly obese patient, the degree of alteration of calcium metabolism is dependent on the length of the common channel constructed. Despite the relatively short period of follow-up, the authors present early signs of a metabolic bone disorder. I would add that the “perfect bariatric operation” remains to be defined for a condition likely due to an inborn error of metabolism. In closing, I have several questions for the authors. (1) Do you have any information on the serum magnesium or bone density, the former of which, namely, the magnesium level, does influence parathormone function? (2) Has any patient presented to date with refractory secondary hyperparathyroidism? (3) Are these patients at risk for oxalate nephrolithiasis, a malady we all have become familiar with?
Finally, Dr Klein’s question about oxalate stones. Two patients in the series did develop renal stones. We did not analyze them because they passed them at home, but we suspect that since the renal calculi developed fairly early on in the postoperative course they were actually caused by dehydration, because sometimes patients find it difficult to drink the same amount of fluid that they normally do when their stomachs are intact. There was no evidence that there was any disorder of calcium metabolism responsible for those renal stones.

Dr Wolfe’s questions: we all know how difficult it is to do calcium balance studies. They are very difficult. We think that the PTH is a very sensitive way of assessing the activity of calcium absorption. We are very aggressive with vitamin D supplementation. The manuscript will tell you that some patients had not only the prenatal vitamin with calcium and vitamin D but we prescribed an additional supplement which we sometimes gave 2 and even 3 times a day. And the patients are in general very compliant because they have to come to us for prescriptions. They get very regular telephone consultations with a dietician. Compliance is probably not an issue that affects our results here.

IN OTHER AMA JOURNALS

JAMA

Hand-Rubbing With an Aqueous Alcoholic Solution vs Traditional Surgical Hand-Scrubbing and 30-Day Surgical Site Infection Rates: A Randomized Equivalence Study

Jean Jacques Parienti, MD, DTM&H; Pascal Thibon, MD; Remy Heller, PharmD, PhD; Yannick Le Roux, MD, DCh; Peter von Theobald, MD, DCh; Hervé Bensadoun, MD, DCh; Alain Bouvet, MD; François Lemarchand, MD, DCh; Xavier Le Coutour, MD; for Members of the Antiseptic Chirurgicale des Mains Study Group

Context Surgical site infections prolong hospital stays, are among the leading nosocomial causes of morbidity, and a source of excess medical costs. Clinical studies comparing the risk of nosocomial infection after different hand antisepsis protocols are scarce.

Objective To compare the effectiveness of hand-cleansing protocols in preventing surgical site infections during routine surgical practice.

Design Randomized equivalence trial.

Setting Six surgical services from teaching and nonteaching hospitals in France.

Patients A total of 4387 consecutive patients who underwent clean and clean-contaminated surgery between January 1, 2000, and May 1, 2001.

Interventions Surgical services used 2 hand-cleansing methods alternately every other month: a hand-rubbing protocol with 75% aqueous alcoholic solution containing propanol-1, propanol-2, and meccetronium etilsulfate; and a hand-scrubbing protocol with antiseptic preparation containing 4% povidone iodine or 4% chlorhexidine gluconate.

Main Outcome Measures Thirty-day surgical site infection rates were the primary end point; operating department teams’ tolerance of and compliance with hand antisepsis were secondary end points.

Results The 2 protocols were comparable in regard to surgical site infection risk factors. Surgical site infection rates were 55 of 2252 (2.44%) in the hand-rubbing protocol and 53 of 2135 (2.48%) in the hand-scrubbing protocol, for a difference of 0.04% (95% confidence interval, −0.88% to 0.96%). Based on subsets of personnel, compliance with the recommended duration of hand antisepsis was better in the hand-rubbing protocol of the study compared with the hand-scrubbing protocol (44% vs 28%, respectively; P = .008), as was tolerance, with less skin dryness and less skin irritation after aqueous solution use.

Conclusions Hand-rubbing with aqueous alcoholic solution, preceded by a 1-minute nonantiseptic hand wash before each surgeon’s first procedure of the day and before any other procedure if the hands were soiled, was as effective as traditional hand-scrubbing with antiseptic soap in preventing surgical site infections. The hand-rubbing protocol was better tolerated by the surgical teams and improved compliance with hygiene guidelines. Hand-rubbing with liquid aqueous alcoholic solution can thus be safely used as an alternative to traditional surgical hand-scrubbing.

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