Eur Spine J (2006) 15: 1005–1014
DOI 10.1007/s00586-005-0975-6

ORIGINAL ARTICLE

Fang-Yeng Chang
Ming-Chau Chang
Shih-Tien Wang
Wing-Kwang Yu
Chien-Lin Liu
Tain-Hsiung Chen

Can povidone-iodine solution be used safely in a spinal surgery?

Received: 7 November 2004
Revised: 18 January 2005
Accepted: 20 May 2005
Published online: 20 August 2005

F.-Y. Chang (✉) · M.-C. Chang
S.-T. Wang · W.-K. Yu · C.-L. Liu
T.-H. Chen
Department of Orthopedics
and Traumatology, Taipei Veterans
General Hospital, Taipei, Taiwan
E-mail: fy_chang@vghtpe.gov.tw
Tel.: +886-2-28757557
Fax: +886-2-28757559

F.-Y. Chang · M.-C. Chang
S.-T. Wang · W.-K. Yu · C.-L. Liu
T.-H. Chen
Department of Surgery,
School of Medicine,
National Yang-Ming University,
Taipei, Taiwan

Abstract Intra-operative incidental contamination of surgical wounds is not rare. Povidone-iodine solution can be used to disinfect surgical wounds. Although povidone-iodine is a good broad-spectrum disinfecting agent, it has occasionally been reported to have a negative effect on wound healing and bone union. Therefore, its safety in a spinal surgery is unclear. A prospective, single-blinded, randomized study was accordingly conducted to evaluate the safety of povidone-iodine solution in spinal surgeries. Ascertained herein was the effect of wound irrigation with diluted povidone-iodine solution on wound healing, infection rate, fusion status and clinical outcome of spinal surgeries. *Materials and methods:* From January 2002 to August 2003, 244 consecutive cases undergoing primary instrumented lumbosacral posterolateral fusion due to degenerative spinal disorder with segmental instability had been collected and randomly divided into two groups: the study group (120 cases, 212 fusion levels) and the control group (124 cases, 223 fusion levels). Excluded were those patients with a prior spinal surgery, spinal trauma, malignant tumor, infectious spondylitis, rheumatoid arthritis, ankylosing spondylitis, metabolic bone disease, skeletal immaturity or with an immunosuppressive treatment. In the former group, wounds were irrigated with 0.35% povidone-iodine solution followed by normal saline solution just before the bone-grafting and instrumentation procedure. However, only with normal saline solution in the latter. All the operations were done by the same surgeon with a standard technique. All the patients were treated in the same postoperative fashion as well. Later on, wound healing, infection rate, spinal bone fusion and clinical outcome were evaluated in both groups. *Results*: A significant improvement of back and leg pain scores, modified Japanese Orthopedic Association function scores (JOA) and ambulatory capacity have been observed in both groups. One hundred and seven patients in the study group and one hundred and nine in the control group achieved solid union. There was no infection in the study group but six deep infections in the control group. Wound dehiscence was noted in one group 1 and two group 2 patients. A subsequent statistical analysis revealed higher infection rate in the control group ($P < 0.05$), but no significant difference in fusion rate, wound healing, improvement of pain score, function score and ambulatory capacity between the two groups. *Conclusion*: Diluted povidone-iodine solution can be used

safely in spinal surgeries, and it will not influence wound healing, bone union and clinical outcome.

Keywords Povidone-iodine solution · Clinical outcome · Spinal bone fusion · Infection

Introduction

Deep infection is a devastating complication in the spinal surgery with reported rates ranging from 0.5 to 13%. The incidence of post-operative spinal infection can be influenced by many factors, and tends to increase generally with complexity of procedure, advanced age, malnutrition, obesity, immunosuppression, remote infection and poor operative environment [20, 22, 43].

Intra-operative contamination of spinal surgical wounds is also a risk factor. Air-borne bacteria in the operation room were considered the main source of wound infection [20]. Contamination happens occasionally with air-borne particles, fallen debris or hair of surgical staff, and is often managed and disinfected with povidone-iodine solution, irrigation (with or without antibiotic solution), pulsatile lavage or parenteral antibiotics [18, 35, 39].

Povidone-iodine solution is widely used in disinfecting open fractures, traumatic and surgical wounds. It is a good disinfecting agent, but the inhibitory effects on osteoblast and fibroblast have been reported in animal studies only [11, 17]. Its safety for clinical use in a spinal surgery therefore hasn't been confirmed yet. The aim in this prospective study was to evaluate the effect of wound irrigation with povidone-iodine on wound healing, infection rate, fusion status and clinical outcome of spinal surgeries.

Materials and methods

The study included 244 consecutive patients of 435 primary instrumented lumbosacral posterolateral fusion levels for degenerative spinal disorder from January 2002 through August 2003 at our institute. They all had lumbar or lumbosacral segmental instability defined by chronic back, buttock and/or leg pain and degenerative spondylolisthesis, degenerative scoliosis or isthmic spondylolisthesis. Patients were excluded from the study if they were with any of the following: a prior spinal surgery, spinal trauma, malignant tumor, infectious spondylitis, rheumatoid arthritis, ankylosing spondylitis, metabolic bone disease, skeletal immaturity and an immunosuppressive treatment.

All the patients were noted on lateral flexion–extension radiographs to have segmental instability (translation of 4 mm and angulation of 10°) [28]. The clinical and neurologic examinations and imaging studies (magnetic resonance imaging) confirmed the levels responsible for the symptoms.

The patients agreeing to participate signed a consent and then were randomly assigned to either treatment group. An independent person unaware of the subject characteristics and study design delivered pre-coded sealed envelopes randomly (containing serial numbers from 1 to 300) to the assignment of the subjects into the two groups. The sealed envelope was not opened until the middle of surgery before wound irrigation. In group 1 composed of patients with odd serial numbers (study group), wounds were irrigated with 0.35% povidone-iodine solution to soak for 3 min, followed by an irrigation with 2000 c.c. of normal saline to remove povidone-iodine solution. No more wound irrigation was given after. The decortication, bone grafting and instrumentation procedures were subsequently performed. In contrast, group 2 with patients even numbered (control group) was wound irrigated only with 2000 c.c. of normal saline.

Group 1 comprised 120 patients (with 212 fusion levels), 64 men and 56 women, at an average age of 67.1 years (20–82 years). Twenty had diabetes mellitus (DM). Sixteen were smokers. Sixty-four took non-steroid anti-inflammatory drugs (NSAIDs) after surgery. The pre-operative diagnosis was degenerative spondylolisthesis in 84, spinal stenosis with instability in 24 and lytic spondylolisthesis in 12. The intended fusion levels were: one level in 56 patients, two levels in 42, three levels in 16 and four levels in 6. A supplementary neural decompression was done in 114 patients (Table 1). As to group 2, it consisted of 59 males and 65 females with 223 fusion levels, at an average age of 65.4 years (22–89 years). Sixteen patients had DM. Twenty-two were smokers. Seventy took NSAIDs after surgery. The pre-operative diagnosis was reported to be degenerative spondylolisthesis in 92, spinal stenosis with instability in 22 and lytic spondylolisthesis in 10. The intended fusion levels were: one level in 54, two levels in 46, three levels in 19 and four levels in 5. A supplementary neural decompression was done in 116. For the other associated factors, please refer to Table 1.

All the operations were performed by the same surgeon with the same technique in standard operating theatres without routine ultraviolet lights for disinfection, laminar flow or body-exhaust suits. The surgical procedures were summarized as follows. The surgery was performed through posterior midline approach with the patient lying in a prone position. The posterior

Table 1 Comparisons of parameters between groups 1 and 2

Epidermiology	Group 1	Group 2	*P* value
Case number (total cases)	120 pts	124 pts	
Gender			
Male	64 cases	59 cases	0.369(NS)*
Female	56 cases	65 cases	
Age[a]	67.1 ± 15.6 years	65.4 ± 12.9 years	0.326(NS)**
Smoking	16 cases	22 cases	0.342(NS)*
DM	20 cases	16 cases	0.407(NS)*
NSAID	64 cases	70 cases	0.625(NS)*
Body mass index[a]	25.8 ± 4.4 kg/m^2	26.6 ± 4.5 kg/m^2	0.186(NS)**
Operative time[a]	223 ± 61 min	211 ± 57 min	0.117(NS)**
Intro-OP blood loss[a]	606 ± 309 ml	572 ± 257 ml	0.352(NS)**
Postoperative drainage[a]	624 ± 400 ml	644 ± 281 ml	0.655(NS)**
Follow-up[a]	19.4 ± 4.1 months	19.1 ± 4.6 months	0.594(NS)**
Etiology			0.753(NS)*
Degerative spondylolisthesis	84 cases	92 cases	
Spinal stenosis with instability	24 cases	22 cases	
Lytic spondylolisthesis	12 cases	10 cases	
Operative levels			0.919(NS)*
Total fusion levels	212 levels	223 levels	
One level			
Above L5-S1	36 cases	37 cases	
Below L5-S1	20 cases	17 cases	
Two levels	42 cases	46 cases	
Three levels	16 cases	19 cases	
Four levels	Six case	5 cases	
Neural decompression	114 cases	116 cases	0.18 (NS)***

* Pearson chi-square test; ** *t*-test; *** Fisher's exact test
[a] Mean and standard deviation

elements (spinous processes, laminae, facet joints and transverse processes) were exposed subperiosteally. Appropriate laminectomy was performed with a facet joint-preserving technique. The entrance point of pedicle screw was identified with anatomic landmarks described by Roy-Camille et al. [33]. The starting point was drilled with a high-speed burr and then the transpedicular canal was formed by probing and tapping through the pedicle into the vertebral body for the placement of a pedicle screw. Gelform plugs were inserted into the pre-drilled channels to prevent excessive blood loss from vertebral body bone marrow. Wound irrigation was completed prior to the bone-grafting and instrumentation procedures. No more wound irrigation was given after this procedure. Decortication of transverse process, pars interarticularis and lateral aspect of facet joints was done with a high-speed burr. The autogenous bone grafts, harvested from the posterior iliac crest and bone chips during the decompression procedure, were packed along the posterolateral gutter. Instrumentation with pedicle screw system via the pre-drilled transpedicular canals was then completed. Wound closure was done layer by layer after the suction drainage was applied.

All patients were treated in the same postoperative manner as described below. A routine analgesic pain control was applied for 3 days. Led by the pre-operative intravenous bolus injections of cefazolin (1000 mg) and gentamicin (60 mg), additional cefazolin (1000 mg/6 h) and gentamicin (60 mg/12 h) were also given for 48 h after the operation, and then oral cefazolin (500 mg/6 h) for 3 days. The drainage tube was removed in 48 or 72 h postoperatively. Then the patient was mobilized with protection of a custom-made lumbosacral orthosis whenever out of bed for 3 months. The orthosis could be removed once per day to allow showering in a standing position.

All patients were followed up 2 weeks, 1 month and 3 months after operation and then every 3 months till the end of study. Clinical outcome, wound status and imaging study, including anteroposterior and lateral radiographs, were checked on every follow-up visit. In addition, lateral flexion–extension bending films and a computed tomography scan were taken to confirm pseudoarthrosis if fusion status was non-union or doubtful. The duration of follow-up was 19.4 months for group 1 and 19.1 months for group 2 (Table 1)

All clinical and radiographic assessments were made by independent observers other than the treating surgeons. Clinical outcome was evaluated by Robinson

Table 2 Fusion grades [19]

Grades	Status	Percent continuity	Motion	Description
0	No fusion	0–<25%	Motion	Discontinuity of the fusion mass with motion
1	Minimal fusion	>25–<50%	Motion	A narrow band of continuity in the fusion mass with motion
2	Moderate fusion	>50–<75%	None	Continuity of the fusion mass without motion
3	Solid fusion	>75–100%	None	Extensive continuity of the fusion mass without motion

pain score, modified Japanese Orthopedic Association function score and ambulatory status [14, 31]. They were taken preoperatively and at the end of study. The severity of back pain and leg pain was graded by the classification of Robinson et al. [31] as: none, no analgesic medication usage; mild, no activity restrictions and occasional use of NSAIDs; moderate, slight limitation of activities and frequent use of non-narcotic analgesics; and severe, regular restriction of activities and use of narcotics for analgesia. The physical function of lower limbs was evaluated with modified JOA functional score and recorded as: point 0, unable to walk; point 1, able to walk with aid; point 2, able to walk without aid but with handrail up or down stairs; point 3, able to walk without aid but inadequate; point 4, no dysfunction [14]. Ambulatory status was evaluated as: point 0, neurogenic claudication with walking distance less than 500 m; point 1, between 500 and 1000 m; point 2, between 1000 and 5000 m; point 3, more than 5000 m. The back and leg pain scores, function scores, and ambulatory status were recorded preoperatively and at the end of study. Differences in scores were taken and analyzed. At the follow-up, the patients were rated in their satisfaction with the results of surgery as very satisfied, somewhat satisfied, somewhat dissatisfied or very dissatisfied.

The fusion status was determined by two independent observers, an orthopedic spine surgeon and a skeletal radiologist, from plain anteroposterior and lateral radiographs at the end of study (at least 1 year after surgery) [40]. The fusion grade was examined at every intended fusion level on both sides, and each level and each side was judged separately. The fusion status was divided into four grades: trabecular bony continuity less than 25% represented grade 0; between 25 and 50%, grade 1; between 50 and 75%, grade 2; more than 75, grade 3 [19]. The fusion status was classified as absence of fusion, provided grades 0 or 1 was noted at the intended fusion level; presence of fusion, in case of grades 2 or 3(Table 2). The lowest grade at intended fusion levels was used for the fusion assessment. Solid union of fusion mass meant that one or both sides had grades 2 or 3 fusion at all intended levels (Fig. 1a, b). If the reported fusion status differed between the examiners, the radiographs were reexamined to reach a consensus. Lateral

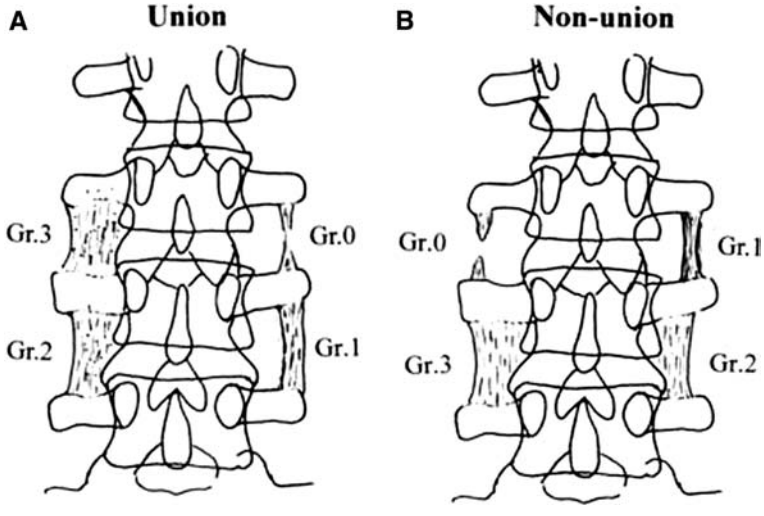

Fig. 1 **a, b** The illustrations showed the assessment of the posterolateral intertransverse spinal fusion. Each level and each side was judged separately. Continuous intertransverse bony bridge (grades 2 or 3 fusion) on at least one of the two sides indicated a fusion at the level. **a** Union meant that one or both sides had grade 2 or grade 3 fusion at all intended levels. **b** *Non-union* indicated that any intended levels had grades 0 or 1 fusion on both sides

flexion–extension radiographs were taken to detect segmental motion (translation of 4 mm and angulation of 10°) if the fusion status was non-union or doubtful (e.g. fusion mass obscured by implant) [28]. Moreover, a computed tomography scan was undertaken to further evaluate any transverse clefts in the fusion mass if segmental motion was noted.

The infections were classified as superficial (above lumbosacral fascia) or deep (below lumbosacral fascia), and as early onset (within 2 weeks postoperatively) or late onset (otherwise). All deep infections were confirmed by laboratory parameters including the erythrocyte sedimentation rate (ESR) and level of C-reactive protein (CRP) and a positive culture of biopsy.

Data were analyzed with a SPSS statistical program (Version 11.0.1, SPSS Inc., IL, USA). All response variables, including demographic characteristics and important outcomes, were measured for all patients. Data were represented as the mean and standard deviation for continuous response variables and as percentages for discrete variables. The Pearson chi-square or Fisher's exact test was used to compare differences between the two groups for each discrete variable; on the other hand, a two-sample *t*-test or Mann–Whitney test for each continuous variable. The Mc Nemar test was used to compare the differences between preoperative and postoperative scores (including pain scores, function scores and ambulatory capacity). Before analysis, the *P* value was set at 0.05 for each test.

Results

There were no statistical differences between both groups with regard to age, gender, DM, smoking, body mass index, the duration of follow-up, pre-operative diagnosis, intended fusion levels, operation time, post-operative drainage or usage of NSAIDs after surgery ($P > 0.05$) (Table 1)

Tables 3 and 4 compare the changes in pain scores from before surgery to the final follow-up between the two groups. In group 1, the preoperative assessment showed that 102 patients had severe or moderate pain in the back or buttock. The postoperative evaluation showed that 106 patients did not have pain or had only mild pain. Ninety-two were rated moderate or severe in pre-operative leg pain. At the final follow-up, 108 patients were rated none or mild in leg pain. As in group 2, the preoperative assessment showed that 101 patients had severe or moderate pain in the back or buttock. The postoperative evaluation showed that 104 did not have pain or had mild pain only. Ninety-five were rated moderate or severe in pre-operative leg pain. At the final follow-up, 110 were rated none or mild in leg pain. The statistical analysis showed a significant reduction in back pain and in leg pain ($P < 0.05$). There was no significant difference between both groups in the distribution of pre-operative and post-operative pain score (Tables 3, 4), nor in the degree of improvement in pain score according to the Mann–Whitney test ($P > 0.05$).

Table 3 The distribution of pre-operative and post-operative back pain score

Severity of pain	Group 1				Group 2				*P* value
	None	Mild	Moderate	Severe	None	Mild	Moderate	Severe	
Preoperative	4	14	56	46	5	18	60	41	NS*
Postoperative	60	46	12	2	55	49	18	2	NS*
P value	S**				S**				
	NS***								

* Pearson chi-square test; ** The improvement of pain scores was examined with Mc Nemar test; *** The differences of the improvement of pain scores between the groups were examined with Mann–Whitney test

Table 4 The distribution of pre-operative and post-operative leg pain score

Severity of pain	Group 1				Group 2				*P* value
	None	Mild	Moderate	Severe	None	Mild	Moderate	Severe	
Preoperative	8	20	54	38	10	19	58	37	NS*
Postoperative	62	46	12	0	59	51	14	0	NS*
P value	S**				S**				
	NS***								

* Pearson chi-square test; ** The improvement of pain scores was examined with Mc Nemar test; ***. The differences of the improvement of pain scores between the groups were examined with Mann–Whitney test

Tables 5 and 6 compare the changes in modified JOA scores and ambulatory capacity from before surgery to the final follow-up between the two groups. In group 1, preoperative function scores showed that 84 patients had significant function impairment. The postoperative evaluation showed that 102 did not have or had mild function limitation. Before surgery, 70 patients walked less than 500 m. At the final follow-up, 91 could walk more than 1000 m. As in group 2, the preoperative assessment showed that 86 patients had significant function impairment. The postoperative evaluation showed that 101 did not have or had mild function limitation. Before surgery, 78 walked less than 500 m. At the final follow-up, 88 could walk more than 1000 m. The statistical analysis showed a significant improvement in function score and in ambulatory capacity ($P < 0.05$). There was no significant difference between both groups in the distribution of pre-operative and post-operative JOA function score and ambulatory capacity (Tables 5, 6), nor in the degree of improvement in JOA score and ambulatory capacity according to the Mann–Whitney test ($P > 0.05$). Eighty-nine percent group-1 patients were reported to be very satisfied or somewhat satisfied with their surgical outcome, whereas 82% for group-2 patients. There was no statistical difference between both groups in the satisfaction with the results of surgery ($P > 0.05$).

Eighty-nine patients in group 1 and 88 in group 2 were classified as fused at all intended levels from plain anteroposterior and lateral radiographs. As to the remaining patients with doubtful or non-fused status, no segmental motion was found in 18 of 31 group-1 patients and 21 of 36 in group-2 after checking lateral flexion-extension radiographs. Computed tomography scans showed transverse clefts in fusion mass in all patients who had segmental motion in lateral flexion–extension radiographs except two group-1 and three group-2 patients in whom the defect of fusion mass was obscured by the metallic artifact caused by the implants. Yet, the motion radiographs did reveal segmental motion; the fusion status of the abovementioned five patients were therefore classified as non-union. As a result, 107 patients in group 1 and 109 in group 2 achieved solid union. Thirteen (10.8%) in group 1 and 15 (12.1%) in group 2 had non-union (Table 7). The difference in the rate of non-union between the two groups was insignificant by the Fisher's exact test ($P = 0.28$). Three patients in group 1 and four in group 2 underwent exploration of the non-union site and re-arthrodesis with autogenous bone graft. Solid union was then achieved in all re-operated patients and satisfactory results were gained in all except persistent back pain was noted in one group 1 patient. Three patients in group 1 and five in group 2 refused any additional surgery. Seven patients in group 1 and six in group 2 had mild symptoms with satisfactory clinical outcomes, and thus took conservative treatment. Junctional stenosis developed in four patients (two group 1, two group 2), requiring a second decompression, instrumentation and arthrodesis. Two patients in

Table 5 The distribution of pre-operative and post-operative modified Japanese Orthopedic Association function score (*JOA*)

	Group 1					Group 2					*P* value
Point	4	3	2	1	0	4	3	2	1	0	
Preoperative	4	32	54	24	6	5	33	49	32	5	NS*
Postoperative	56	46	14	4	0	50	51	15	8	0	NS*
P value	S**					S**					
	NS***										

* Pearson chi-square test; ** The improvement of function scores was examined with Mc Nemar test; *** The differences of the improvement of function scores between the groups were examined with Mann–Whitney test

Table 6 The distribution of pre-operative and post-operative ambulatory capacity

Walking distance	Group 1				Group 2				*P* value
	< 0.5 km	0.5–1 km	1–5 km	> 5 km	< 0.5 km	0.5–1 km	1–5 km	> 5 km	
Preoperative	70	32	10	8	78	25	12	9	NS*
Postoperative	10	19	47	44	15	21	49	39	NS*
P value	S**				S**				
	NS***								

* Pearson chi-square test; ** The improvement of walking distance was examined with Mc Nemar test; *** The differences of the improvement of walking distance between the groups were examined with Mann–Whitney test

Table 7 Infection rate and union rate

	Group 1	Group 2	*P* value
Infection	0 case	Six cases (4.8%)	0.029(S)*
Union	107 cases (89.1%)	109 cases (87.9%)	0.457(NS)*

*Fisher's exact test

group 1 and one in group 2 had dura tear and were treated with repair with 8-O nylon. There were no new peripheral neurologic deficits associated with pedicle screws after surgery in both groups.

There was no wound infection in group 1 during the follow-up period, but two early onset and four late-onset deep infections (4.8%) in group 2. Among these six cases, methicillin-resistant *Staphylococcus aureus* (MRSA) was cultured from five cases, whereas Enterobacter cloacae was grown on one culture. After the treatment of radical debridement and parenteral antibiotics (according to sensitivities) for 6 weeks and oral antibiotics for 2 months, a satisfactory outcome has been reached except in two cases. In these two remaining deep infections, the implants were removed 4 months postoperatively, because debridement alone was not enough to eradicate the infection. With persistent severe back pain and poor ambulation after surgery, these two patients were very dissatisfied with the result of surgery. At the other aspect, the wound dehiscence was found in one group 1 and two group 2 patients, yet all healed after a debridement and reclosure procedure. No microorganisms grew in the cultures taken before the administration of antibiotics from the wounds in these three patients. The others healed well and the sutures were removed on the 14th post-operative day.

Discussion

Deep infection is a devastating complication in a spinal surgery. Amongst all infective organisms, *S. aureus* is the most common one. The current prophylactic antibiotics, the first-generation or second-generation cephalosporin and aminoglycoside, can effectively reduce the infection rate related to low-virulence *S. aureus* and other organisms. Unfortunately, most of the serious nosocomial infective organisms, such as MRSA and *Pseudomonas aeroginosa*, are resistant to these first-line antibiotics [20, 22, 43]. Moreover, the incidence of methicillin-resistant organisms has been found to have a trend of increasing. For instance, Klekamp et al. have reported 16 postoperative spinal infections (with a rate of 45%) caused by MRSA in 35 patients. From their observation, the risk factors of MRSA infection might include lymphopenia, chronic infection, alcohol abuse and recent hospitalization [13].

Intra-operative contamination of a surgical wound is also an important cause for postoperative spinal infection [20]. Antibiotics and antiseptics irrigation of surgical wounds has been used to decrease the associated infection rates. Many in vitro and animal studies, for example, indicated the effectiveness of topical antibiotics in eliminating causative organisms in surgeries [32, 34]. However, the clinical study for orthopedic surgery is sparse. In a review of topical antibiotics prophylaxis, Haines suggested that intraoperative topical antibiotics would be beneficial for surgical wounds with high infection risk (greater than 15%), but no sound scientific evidence for wounds with a risk of infection less than 5% [8]. Besides, there are two clinical reports investigating the effectiveness of topical antibiotic instillation without the addition of systemic antibiotics in an orthopedic surgery. Within these two, Maguire (using a bacitracin/neomycin powder) found topical agents were effective in reducing infection rates, while Nachamie (using dilute neomycin) found them ineffective [21, 25]. In conclusion, it may be said that data are currently too insufficient to justify the effectiveness of topical antibiotics for prevention of postoperative infection.

Povidone-iodine solution, with concentration of 10%, is a broad-spectrum disinfecting agent that would not generate resistance in microorganisms, even in the case of antibiotics or antiseptics cross-resistance [15, 37]. Maximally effective at the 1:100 dilution, it still retains bactericidal activity even at 1:10,000. The apparent bactericidal potency increase of diluted povidone-iodine solution consists in the density increase of "free" iodine, to a maximum of approximately 26 ppm between 0.1 and 1% povidone-iodine [9]. Some have reported that iodine preparations are generally de-activated by organic substances and proteins, but Kunisada et al. found that 0.2 and 0.5% diluted povidone-iodine solution could kill the bacteria completely even in the presence of 5 and 10% serum, respectively [15]. In a large perspective study on the etiology of spondylodiscitis after microscopic discectomy, Tronnier et al. [41] have demonstrated that 17% (70 out of 412) of their patients had a positive bacteriological culture from their intervertebral disc space during operation. Yet routine application of povidone-iodine or neomycin sulfate solution into the disc space at the end of operation could reduce the infection rate to 0.25% (1 out of 412). Povidone-iodine solution can decontaminate the operative site and prevent clinical infection despite positive culture findings. Nevertheless, the influence of povidone-iodine on a wound and clinical outcome has not been mentioned.

Povidone-iodine solution is widely used in disinfecting traumatic and surgical wounds. In in vitro and

in vivo animal studies, although the inhibitory effect of povidone-iodine on fibroblast and wound healing has been reported to be positive, wound healing process, wound tensile strength and re-epithelization were not affected in experimental corneal defects and skin wounds [2, 7, 24, 26]. Despite that the results from in vitro and in vivo animal experiments might not be simply applied to human, wound healing was not influenced negatively by povidone-iodine in normal skin (suction blister and surgical wound) or disturbed one (burns and Mohs' therapy) in many human studies [6, 7, 30]. In our study, only one wound dehiscence was noted after irrigation with diluted povidone-iodine solution.

Although povidone-iodine solution is widely used in disinfecting open fractures, traumatic and surgical wounds, its safety in orthopedic surgery remains controversial. No literature has ever reported its effect on human spinal bone fusion. In one animal study, however, Kaysinger et al. [11] exposed embryo chick osteoblast and tibia bone to diluted Betadine solution (at a concentration of 0.5, 5, 50 and 100%, respectively) and found that povidone-iodine was cytotoxic to chick osteoblast and tibia at the concentration of more than 0.5% povidone-iodine solution. Yet, no cytotoxic effect was noted at lower concentration (0.05%). Judging from what can be referenced, we irrigated the surgical wound with diluted povidone-iodine solution at the concentration of 0.35%, which could eradicate the bacteria and reduce the inhibitory effect on fibroblast and osteoblast to the minimum [15].

Pseudarthrosis often is associated with poor clinical results [10, 42]. The non-union rate of instrumented posterolateral fusion ranges from 7 to 28%, and is related to the number of fused levels, smoking, age, osteoporosis, malnutrition and radiotherapy [4, 16, 27, 38, 44]. The incidence of non-union (11% for group 1 and 12% for group 2) in our study is comparable with previous reports [5, 10]. The difference between both groups in the rate of union, improvement of pain score and function score was not significant according to the Fisher's exact test and Mc Nemar test. These results showed the absence of strongly negative effect of diluted povidone-iodine irrigation on spinal fusion and clinical outcome. Povidone-iodine solution seems not to alter the microvessels but can enhance angiogenesis, which is essential in bone healing [1, 6, 12]. Macrophages play a central role in wound healing by removing necrotic debris in wound and secreting cytokines and growth factors, which regulate mesenchymal stem cell recruitment, proliferation and differentiation [29]. They also play a similar pivotal role in osseous healing by producing bone morphogenetic proteins (e.g. BMP-2, BMP-6) and transforming growth factor-β-1 to promote human mesenchymal stem cell (hMSC) differentiation along the osteoblastic lineage for new bone formation [3, 36]. As povidone-iodine solution may activate macrophages, modulate their cytokine output and generate an influx of monocytes and T-lymphocytes into the wound, it may be beneficial in bone healing [23]. Besides, the povidone-iodine-soaked cortex was burred away before the bone-grafting procedure, which made the local bone marrow (the major source of osteoprogenitor and inflammatory cells) uninfluenced, thus to reduce the inhibitory effect of povidone-iodine solution on osteoblast and osteogenesis.

One may doubt the irritation effect of povidone-iodine solution on wounds and nerves. The assessment of severity of pain tends to be subjective, thus hard to evaluate. Due to routine use of postoperative analgesic pain control, the immediate postoperative pain score ends up complicated to evaluate. As no significant difference was found between both groups in wound healing and pain score throughout the follow-up evaluation, it seemed that irrigation with diluted povidone-iodine solution followed by normal saline did not cause significant wound irritation or deteriorate clinical outcomes.

With the sub-optimal operative environment, which did not include ultraviolet light for disinfection, laminar flow or body-exhaust systems, the deep infection rate (4.8%) in group 2 was higher than those reported elsewhere [20, 22, 43]. In group 1, with wound irrigation by additional diluted povidone-iodine, no wound infection developed. The difference in the infection rates was statistically significant between the two groups ($P = 0.029$). Except the use of povidone-iodine irrigation, no other factors differed between the two groups. It does not necessarily mean that the diluted povidone-iodine irrigaion alone will prevent postoperative infection, but rather such irrigation does aid in combination with the preventive measures like intraoperative aseptic techniques, diligent surgical procedures and parenteral antibiotics. This effectiveness might be more meaningful in a relatively poorer preoperative environment.

In conclusion, wound irrigation with diluted povidone-iodine solution followed by normal saline before the bone-grafting procedure exerted no negative effects on spinal bone fusion, clinical outcome and wound healing. Diluted povidone-iodine solution can be used safely in a spinal surgery for the prevention of postoperative spinal infection, especially in patients with the wound contaminated accidentally during operation, or in an inappropriate environment without routine ultraviolet lights for disinfection, laminar flow or body-exhaust suits.

Acknowledgements The manuscript does not contain information about medical device(s)/drug(s). No funds were received in sup-

port of this work. No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this manuscript. We thank Miss Hui-Chen Lee, Division of Experimental Surgery, for her help in stastistic analysis.

References

1. Abbey DM, Turner DM, Warson JS et al (1995) Treatment of postoperative wound infections following spinal fusion with instrumentation. J Spinal Disord 4:278–283
2. Branemark PI, Ekholm E (1967) Tissue injury caused by wound disinfectants. J Bone Joint Surg Am 49A:48–62
3. Champagne CM, Cooper LF, Offenbacher S et al (2002) Macrophage cell lines produce osteoinductive signals that include bone morphogenetic protein-2. Bone 30(1):26–31
4. Emery SE, Hughes SS, Junglas WA et al (1994) The fate of anterior vertebral bone grafts in patients irradiated for neoplasm. Clin Orthop 300:207–212
5. Fischgrund JS, Machay M, Herkowitz HN et al (1997) Degenerative lumbar spondylolisthesis with spinal stenosis: a prospective, randomized study comparing decompressive laminectomy and arthrodesis with and without spinal instrumentation. Spine 22:2807–2812
6. Fumal I, Braham C, Paquet P et al (2002) The beneficial toxicity paradox of antimicrobials in leg ulcer healing impaired by a polymicrobial flora: a proof-of-concept study. Dermatology 204S1:70–74
7. Gruber R, Vistnes L, Pardoe R (1975) The effect of commonly used antiseptics on wound healing. Plast Reconstr Surg 55:472–476
8. Haines SJ (1982) Topical antibiotic prophylaxis in neurosurgery. Neurosurgery 11(2):250–253
9. Haley CE, Marling-Cason, Smith JW et al (1985) Bactericidal activity of antiseptics against methicillin-resistant stapholococcus aureus. J Clin Microbiol 21(6):991–992
10. Jackson RK, Boston DA, Edge AJ (1985) Lateral mass fusion. A prospective study of a consecutive series with long-term follow-up. Spine 10:828–832
11. Kaysinger KK, Nicholson NC, Ramp WK et al (1995) Toxic effects of wound irrigation solutions on cultured tibiae and osteoblasts. J Orthop Trauma 9(4):303–311
12. Kjolseth D, Barker JH, Barker JH et al (1994) Comparison of the effects of commonly used wound agents on epithelialization and neovascularization. J Am Coll Surg 179:305–312
13. Klekamp J, Spengler DM, McNamara MJ et al (1999) Risk factors associated with methicillin-resistant staphylococcal wound infection after spinal surgery. J Spinal Disord 12(3):187–191
14. Kozo Okada, Shiro Oka, Kenji Tohge et al (1991) Thoracic myelopathy caused by ossification of the ligamentum flavum. Spine 16:280–287
15. Kunisada T, Yamada K, Hara O et al (1997) Investigation on the efficacy of povidone-iodine against antiseptic-resistant species. Dermatology 195S2:14–18
16. Lenke LG, Bridwell KH, Blanke K et al (1995) Prospective analysis of nutritional status normalization after spinal reconstructive surgery. Spine 20:1359–1367
17. Lineaweaver W, Howard R, Soucy D et al (1985) Topical antimicrobial toxicity. Arch Surg 120:267–270
18. Lineaweaver W, McMorris S, Soucy D et al (1985) Cellular and bacterial toxicities of topical antimicrobials. Plast Reconstr Surg 75:394–396
19. Linovitz RJ, Pathria M, Bernhardt M et al (2002) Combined magnetic fields accelerate and increase spine fusion. Spine 12:1383–1389
20. Lonstein J, Winter R, Moe J et al (1973) Wound infection with Harrington instrumentation and spine fusion for scoliosis. Clin Orthop 96:222–233
21. Maguire WB (1964) The use of antibiotics, locally and systemically, in orthopedic surgery. Med J Aust 12(52):412–414
22. Massie JB, Heller JG, Abitbol JJ et al (1992) Postoperative posterior spinal wound infections. Clin Orthop 284:99–108
23. Moore K, Thomas A, Harding KG (1997) Iodine released from the wound dressing iodosorb modulates the secretion of cytokines by human macrophages responding to bacterial lipopolysaccharide. Int J Biochem Cell Biol 29(1):163–171
24. Mulliken J, Healey N, Glowacki J (1980) Povidone-iodine and tensile strength of wounds in rats. J Trauma 20:323–324
25. Nachmie BA, Siffert RS, Bryer MS (1968) A study of neomycin instillation into orthopedic surgical wounds. JAMA 204:687–689
26. Niedner R (1997) Cytotoxicity and sensitization of povidone-iodine and other frequently used anti-infective agents. Dermatology 195S2:89–92
27. Nilsson OS, Bauer HCF, Brostrom LA (1987) Methotrexate effects on heterotopic bone in rats. Acta Orthop Scand 58:47–53
28. Penning L, Blickman JR (1980) Instability in lumbar spondylolisthesis: a radiologic study of several concepts. AJR Am J Roentgenol 134:293–301
29. Rappolee DA, Werb Z (1992) Macrophage-derived growth factors. Curr Top Microbiol Immunol 181:87–140
30. Robbins P, Day CL Jr, Lew RA (1984) A multivariate analysis of factors affecting wound-healing time. Dermatol Surg Oncol 10:219–222
31. Robinson RA, Walker AE, Ferlic DC et al (1962) The results of anterior interbody fusion of the cervical spine. J Bone Joint Surg 44A:1569–1587
32. Rosenstein BD, Wilson FC, Funderburk CH (1989) The use of bacitracin irrigation to prevent infection in postoperative skeletal wounds. J Bone Joint Surg Am 70A:427–430
33. Roy-Camille R, Saillant G, Mazel C (1986) Internal fixation of the lumbar spine with pedicle screw plating. Clin Orthop 203:7–17
34. Scherr DD, Dodd TA (1976) In vitro bacteriological evaluation of the effectiveness of antimicrobial irrigation solutions. J Bone Joint Surg Am 58A:119–122
35. Scherr DD, Dodd TA, Buckingham WW Jr (1972) Prophylactic use of topical antibiotic irrigation in uninfected surgical wounds. J Bone Joint Surg Am 54A:634–640
36. Schmitt JM, Hwan K, Winn SR et al (1999) Bone morphogenetic proteins: An update on basic biology and clinical relevance. J Orthop Res 17:269–278
37. Schreier H., Erdos G, Fleischer W et al (1997) Molecular effects of povidone-iodine on relevant microorganisms: an electron-microscopic and biochemical study. Dermatology 195S2:111–116
38. Silcox DH, Daftari D, Boden SD et al (1995) The effect of nicotine on spinal fusion. Spine 20:1549–1553

39. Sindelar WF, Mason GR (1977) Efficacy of povidon-iodine irrigation in prevention of surgical wound infections. Surg Forum 28:48–51
40. Steinmann JC, Herkowitz HN (1992) Pseudarthrosis of the spine. Clin Orthop 284:80–89
41. Tronnier V, Schneider R, Kunz U et al (1992) Postoperative spondylodiscitis after operation for lumbar disc herniation. Acta Neurochirurgica 117:149–152
42. Vaughan PA, Malcolm BW, Maistrelli GL (1988) Results of L4-L5 disc excision alone versus disc excision and fusion. Spine 13:690–699
43. Wimmer C, Gluch H, Franzreb M et al (1998) Predisposing factors for infection in spine surgery: a survey of 850 spinal procedures. J Spinal Disord 11(2):124–128.
44. Zdeblick TA (1993) A prospective, randomized study of lumbar fusion—-preliminary results. Spine 18:983–991