



**Australian Government**  
**Department of Health and Ageing**



# Horizon Scanning Technology Prioritising Summary

## Supplemental perioperative oxygen to reduce the risk of surgical wound infection

February 2007



**Australian  
Safety  
and Efficacy  
Register  
of New  
Interventional  
Procedures -  
Surgical**



**Royal Australasian  
College of Surgeons**

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The production of this Horizon scanning prioritising summary was overseen by the Health Policy Advisory Committee on Technology (HealthPACT), a sub-committee of the Medical Services Advisory Committee (MSAC). HealthPACT comprises representatives from health departments in all states and territories, the Australia and New Zealand governments; MSAC and ASERNIP-S. The Australian Health Ministers' Advisory Council (AHMAC) supports HealthPACT through funding.

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# PRIORITISING SUMMARY

**REGISTER ID:** S000012

**NAME OF TECHNOLOGY:** SUPPLEMENTAL PERIOPERATIVE OXYGEN

**PURPOSE AND TARGET GROUP:** TO REDUCE THE RISK OF SURGICAL WOUND INFECTION

**STAGE OF DEVELOPMENT (IN AUSTRALIA):**

- |   |   |
|---|---|
| <input checked="" type="checkbox"/> Yet to emerge | <input type="checkbox"/> Established  |
| <input type="checkbox"/> Experimental             | <input type="checkbox"/> Established <i>but</i> changed indication or modification of technique |
| <input type="checkbox"/> Investigational          | <input type="checkbox"/> Should be taken out of use   |
| <input type="checkbox"/> Nearly established       |   |

**AUSTRALIAN THERAPEUTIC GOODS ADMINISTRATION APPROVAL**

- |  |             |     |
|--|-------------|-----|
| <input type="checkbox"/> Yes                       | ARTG number | N/A |
| <input type="checkbox"/> No                        |             |     |
| <input checked="" type="checkbox"/> Not applicable |             |     |

**INTERNATIONAL UTILISATION:**

COUNTRY	LEVEL OF USE		
	Trials Underway or Completed	Limited Use	Widely Diffused
Spain	✓		
United States	✓		
Austria	✓		

**IMPACT SUMMARY:**

The procedure, if found to be beneficial, would be conducted by anaesthesiologists to reduce the incidence of surgical site infections.

## **BACKGROUND**

Surgical site infection (SSI) is possibly the most common serious complication of surgery and anaesthesia (Belda et al. 2005). In addition to the increased morbidity and mortality in patients with SSIs, previous studies have shown that SSIs can prolong hospitalisation by 5 to 20 days, resulting in substantial increases in cost (Grief et al. 2000). The human body's primary defence against surgical pathogens is oxidative killing by neutrophils, a process dependent on the production of bactericidal superoxide radicals from molecular oxygen. The rate of this reaction is reliant on the partial pressure of oxygen in tissue. In the case of neutrophils, oxidative killing depends on a partial pressure in the range from 0 to > 300 mmHg (Grief et al. 2000). Studies have shown that all wounds cause disruption of vascular supply, causing the wound site to be hypoxic compared to normal tissue. Based on these findings, researchers have hypothesised that resistance to infection can potentially be improved by increasing arterial oxygen tension beyond that required to saturate blood. Therefore supplemental administration of oxygen during the perioperative period has been investigated as a potential method of reducing SSIs (Grief et al. 2000).

It is important to note that the increased production of reactive oxygen species due to high oxygen partial pressure may cause substantial deleterious effects as well. Reactive oxygen species are involved in some processes that produce tissue injury and inhibit antibacterial mechanisms. Studies have shown that reactive oxygen species are capable of causing cellular dysfunction by damaging DNA and proteins and by increasing lipid peroxidation, which may lead to cell death via apoptosis or necrosis (Pryor et al. 2004).

## **CLINICAL NEED AND BURDEN OF DISEASE**

Clinical data has shown that between 5% and 10% of patients admitted to hospital will acquire an infection during their admission. In Australia, the National Nosocomial Prevalence Survey (1984) revealed that 6.3% of 28,643 hospitalised patients had a hospital-acquired infection, with the highest rates in larger hospitals. Meanwhile, recent studies conducted in the United States have suggested that the rate of hospital-acquired infections has increased over the past two decades (Spelman 2002). SSIs have been found to occur in up to 10% of patients undergoing clean surgery with the incidence varying with the complexity of surgery, intrinsic patient risk and surgical skills. The common clinical features of surgical wound infection are localised pain, redness and discharge (Spelman 2002).

## **DIFFUSION**

It is not known if perioperative supplementation of oxygen is currently being utilised widely in any part of the world. In Australia, there is no evidence that this procedure has been adopted as standard procedure within the healthcare system.

## **COMPARATORS**

The most critical factors in the prevention of SSIs, although difficult to quantify, are the sound judgment and proper technique of the surgeon and surgical team, as well as the general health and disease state of the patient. Other factors that may influence the development of SSIs, especially in clean surgical procedures, include airborne exogenous microorganisms (Nichols 2001). There are no direct comparators for supplemental perioperative oxygen, other than conventional antimicrobial prophylaxis.

## **SAFETY AND EFFECTIVENESS ISSUES**

The first randomised controlled trial conducted to examine the safety and effectiveness of perioperative oxygen supplementation for the reduction of SSIs was conducted by Grief et al. (2000). In this trial, a total of 500 patients undergoing elective open colorectal resection were

randomly allocated to receive 30% oxygen and 70% nitrogen (250 patients) or 80% oxygen and 20% nitrogen (250 patients). Immediately before extubation, oxygen was increased to 100% in both patient groups. Following extubation, the oxygen concentration was returned to its previous levels and was maintained during the first 2 hours of recovery. The investigators reported that arterial oxygen saturation and partial pressure of arterial oxygen were significantly higher intraoperatively in patients who received 80% oxygen. In addition, subcutaneous oxygen tension was significantly higher during and after surgery in patients who received 80% oxygen. For both patient groups, the overall incidence of surgical wound infection was 8%, slightly higher than the predicted NNIS<sup>1</sup> scale. Risk of infection was similar in both groups based on SENIC<sup>2</sup> and NNIS scales. However, the actual occurrence of SSI was 13 patients (5.2%, 95% CI 2.4-8.0%) in the 80% oxygen group and 28 patients (11.2%, 95% CI 7.3-15.1%) in the 30% oxygen group. The absolute difference in rates of infection between the groups was 6.0% (95% CI 1.2-10.8%). Mean ASEPSIS<sup>3</sup> wound scores were higher in patients given 30% oxygen ( $5 \pm 9$ ) compared to patients given 80% oxygen ( $3 \pm 7$ ) ( $p = 0.01$ ). A total of 12 patients from the 30% oxygen group were admitted into the intensive care unit while 5 patients from the 80% oxygen group were admitted ( $p = 0.14$ , not significant). Of the parameters analysed, only the use of 30% oxygen correlated significantly with the risk of infection in the mixed-effects model, with an odds ratio of 2.3 (95% CI 1.2-4.6). Patients that succumbed to infection had their staples removed one day later compared to those without infection ( $p < 0.001$ ) and their duration of hospitalisation was prolonged by one week ( $p < 0.001$ ) (Grief et al. 2000).

Following the trial conducted by Grief et al. (2000), Pryor et al. (2004) conducted a similar randomised trial with 165 patients undergoing major intra-abdominal surgical procedures. Of the 165 patients, 160 were included for analysis (80 received 35% oxygen and the remaining 80 received 80% oxygen). However despite implementing similar protocols, Pryor and colleagues reported markedly different results compared to Grief et al. (2000). Overall, a total of 29 patients suffered from SSI, nine patients (11.3%) from the 35% oxygen group and 20 patients (25%) in the 80% oxygen group. The odds ratio for the two groups was 2.63 (Wald 95% CI 1.1-6.2) and the risk ratio was 2.22 (95% CI 1.1-4.6). As expected, patients with SSIs had significantly longer hospitalisation ( $p < 0.001$ ). The authors reported that the length of hospitalisation was longer in the 80% oxygen group but this did not reach significance ( $p = 0.07$ ). All of the four patients with SSI that required reoperation, were from the 80% oxygen group. In the multivariate logistic regression analysis, the fractional inspired concentration of oxygen was predictive of infection ( $p = 0.03$ ) (Pryor et al. 2004). It should be noted that this study did not specify the baseline infection rate that was utilised, therefore the investigators estimate that 300 patients would be required to detect a 40% reduction in the infection rate is not possible to confirm. Belda et al. (2005) states that the study by Pryor et al. (2004) appears to be underpowered and that this was further compounded by stopping the study after only 160 patients were randomised (*a priori* stopping point which was only 53.3% of the anticipated sample size). Furthermore, the patients enrolled into the study by Pryor et al. (2004) were not homogenous, which is evident from the fact that patients who received 80% oxygen had significantly higher BMIs ( $p = 0.04$ ) and the number of obese patients in each group was significantly different ( $p = 0.04$ ). In addition, patients who received 80% oxygen had significantly greater blood loss ( $p = 0.03$ ) and received a greater volume of crystalloid

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<sup>1</sup> NNIS: The National Nosocomial Infection Surveillance System predicts risk on the bases of type of surgery, rating of physical status and the duration of surgery. Higher scores indicate greater infection risk.

<sup>2</sup> SENIC: The Study on the Efficacy of Nosocomial Infection Control evaluates risk of infection by assigning one point to each of the following factors: three or more underlying diagnoses at discharge, surgery that lasts two or more hours, an abdominal site of surgery and the presence of a contaminated or infected wound. Higher scores indicate greater infection risk.

<sup>3</sup> ASEPSIS: Healing and infection score. Higher scores indicate poorer healing and greater risk of infection.

( $p = 0.02$ ). However, Pryor et al. (2004) declared that BMI, obesity and blood loss were not predictors of infection in the multivariate analysis conducted.

In view of the conflicting results presented by Grief et al. (2000) and Pryor et al (2004), Belda et al. (2005) re-examined the safety and efficacy of perioperative oxygen supplementation in 300 patients undergoing elective colorectal surgery. Patients were randomly allocated to 30% or 80% oxygen levels and continued to receive the allocated level of oxygen during the first 6 hours of recovery. A total of 9 patients were excluded, leaving 291 patients for analysis (143 patients received 30% oxygen, the remaining 148 received 80% oxygen). Overall, 57 patients (39.3%) were diagnosed with SSIs, 35 patients (24.4%) from the 30% oxygen group and 22 patients (14.9%) from the 80% oxygen group ( $p = 0.04$ ). The risk of SSI was found to be 39% lower in the 80% oxygen group (relative risk: 0.61, 95% CI 0.38-0.98) compared to patients who received 30% oxygen. When this analysis included 5/9 patients who were excluded (4 patients were excluded based on a priori exclusion criteria and hence will not be considered) and who were assumed to have not developed SSI, the relative risk reduction was 0.62 (95% CI 0.38-1.00;  $p = 0.05$ ) in patients who received 80% oxygen. Other outcomes such as time to staple removal and duration of hospitalisation were not significantly different between the patients groups. Two patients, both from the 30% oxygen group, died due to multiorgan failure of septic origin. Overall, patients with infection took longer to ambulate ( $p = 0.008$ ), had staples removed later ( $p = 0.007$ ) and had prolonged hospitalisation ( $p = 0.001$ ). Unadjusted analyses revealed that men and those with coexisting respiratory diseases were at greater risk of SSI. Following multivariate adjustment, the percentage of inspired oxygen and coexisting respiratory diseases were significantly associated with increased risk of infection. Adjustment for all covariates revealed a 54% reduction in risk of SSI in patients assigned to 80% oxygen (relative risk: 0.46; 95% CI 0.22-0.95;  $p = 0.04$ ), while patients with coexisting respiratory disease had a 3.23-fold (95% CI 1.18-8.86) greater risk of developing SSI.

In a smaller randomised controlled trial involving 38 patients (19 patients received 80% oxygen, 19 patients received 30% oxygen) undergoing elective colorectal cancer surgery, Mayzler et al. (2005) reported that the incidence of SSIs was similar in both treatment groups ( $p = 0.53$ ). Therefore, supplemental oxygen resulted in no reduction in SSIs in this study, which did however have a relatively small patient cohort and may have been underpowered (Mayzler et al. 2005).

## **COST IMPACT**

Research has shown that postoperative infections in patients with cancer add an average of USD\$12,500 per patient to the cost of care (Grief et al. 2000). In another example, a SSI after a coronary artery bypass graft added an average of \$12,419 to the cost of the procedure, which further increased to \$31,597 if the infection was a deep sternal wound infection (Spelman 2002). It is therefore clear the SSIs can lead to substantial increases in cost. Two of the three included randomised controlled trials in this summary support the use of perioperative oxygen supplementation to reduce SSIs. If this procedure is conclusively proven to be safe and effective, it will undeniably result in large cost reductions in the healthcare system.

The Medicare Benefits Schedule reimbursement fees related to surgical infections are listed in Table 1:

**Table 1 Medical Benefits Schedule of fees for procedures related to surgical infection (Medicare Australia 2006)**

Category	Item Number	Benefit (AUD)	Number of Claims (July 2005 to June 2006)
Reoperation on sternum for dehiscence or infection involving reopening of the mediastinum, with or without rewiring.	38466	\$846.55	125
Reoperation for infection of sternum or mediastinum involving muscle advancement flaps or greater omentum.	38468	\$1304.45	28
Reoperation for infection of sternum or mediastinum involving muscle advancement flaps <i>and</i> greater omentum.	38469	\$1520.65	6
Drainage of intracranial infection via burr-hole - including burr-hole.	39900	\$458.50	15
Open operation and drainage for infection of flexor tendon sheath of finger or thumb.	46522	\$372.20	162

### **ETHICAL, CULTURAL OR RELIGIOUS CONSIDERATIONS**

No issues were identified from the retrieved material.

**OTHER ISSUES** No issues were identified from the retrieved material.

### **HEALTHPACT CONCLUSION**

The evidence currently available for perioperative oxygen supplementation is of high quality (level II intervention evidence); however the conflicting results reported suggest caution be taken. HealthPACT has recommended that further assessment of this technology is no longer warranted.

- |  |  |
|--|--|
| <input type="checkbox"/> Horizon Scanning Report | <input type="checkbox"/> Full Health Technology Assessment |
| <input type="checkbox"/> Monitor                 | <input checked="" type="checkbox"/> Archive                |
| <input type="checkbox"/> Refer                   | <input type="checkbox"/> Decision pending                  |

### **SOURCES OF FURTHER INFORMATION:**

Roos D, Bruggen RV, Meischl C. Oxidative killing of microbes by neutrophils. *Microbes and Infection* 2003; 5(14): 1307-1315.

### **LIST OF STUDIES INCLUDED**

Total number of studies            3  
 Level II intervention evidence

### **SEARCH CRITERIA TO BE USED:**

Oxygen/therapeutic use\*  
 Surgical wound infection/prevention & control\*  
 Perioperative oxygen

Surgical site infection  
Supplement oxygen

**REFERENCES:**

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Spelman DW. MJA Practice Essentials: Hospital-acquired infections. *Medical Journal of Australia* 2002; 176(6): 286-291.