review

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# Hydrogen peroxide ($H_2O_2$): a review of its use in surgery

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**Summary** Hydrogen peroxide has been used in medicine for more than 100 years. It is known in surgery as a highly useful irrigation solution by virtue of both its hemostatic and its antimicrobial effects. Due to its possible negative effect on wound healing and its cytotoxic effect in higher concentrations, there are concerns about the safety of its use. The objective of this paper is to review the safety and beneficial effects of hydrogen peroxide.

**Keywords** Hydrogen peroxide · Irrigation solution · Cytotoxicity · Antimicrobial · Wound healing

## Wasserstoffperoxid ($H_2O_2$) – eine Übersicht zur Verwendung in der Chirurgie

**Zusammenfassung** Wasserstoffperoxid wird in der Medizin seit über 100 Jahren benutzt. In der Chirurgie wird es wegen seiner hämostatischen und antimikrobiellen Wirkung als Spüllösung verwendet. Aufgrund der möglichen negativen Auswirkungen auf die Wundheilung und wegen der Zytotoxizität in höheren Konzentrationen gibt es Bedenken in Bezug auf die Sicherheit der Nutzung. Im vorliegenden Beitrag sollen die Sicherheit und die positiven Wirkungen von Wasserstoffperoxid überprüft werden.

**Schlüsselwörter** Wasserstoffperoxid · Spüllösung · Zytotoxizität · Antimikrobiell · Wundheilung

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## Introduction

Hydrogen peroxide (HP) in its pure form is a light blue, in its diluted form a colorless, odorless water-soluble liquid that consists of hydrogen and oxygen. Its molecular formula is $H_2O_2$. Other names include perhydroxic acid, dioxidane, and oxydanyl.

HP was first synthesized in 1818 by Louis Jacques Thénard by reacting nitric acid with barium peroxide. Nowadays, it is produced by the anthraquinone process, whereby anthrahydroquinone is reacted with oxygen under pressure to extract hydrogen peroxide and anthraquinone, which can be reduced to anthrahydroquinone again.

HP is an oxidizing agent and is commonly found in cosmetics, bleaching agents, toothpaste, and detergents. It is very unstable and reacts on contact with oxidizable organic matter, metal, and in alkaline solutions by producing free hydroxyl radicals, which react with lipids, proteins, and DNA. Catalysts, light, motion, and temperature promote its degradation.

## Medical use

HP is medically used as an antiseptic solution for disinfection and wound irrigation. In the medical setting, one commonly finds 3% and 30% concentrated solu-

tions. These can be diluted with saline solution to any desired concentration.

HP has been used in dentistry as a mouth wash to reduce plaque and to improve recovery after oral surgery for more than 100 years [1].

## Antiseptic/antibacterial effect

HP is an antiseptic and antibacterial agent that provides broad-spectrum efficacy against both gram-positive and gram-negative bacteria, bacterial spores, viruses, and yeast. Greater antibacterial activity is seen against gram-positive compared with gram-negative bacteria. The level of catalase and other peroxidases in these organisms can cause increased tolerance to HP and may make HP solutions under 3% less effective [2, 3]. The antiseptic effect is mainly determined by the $H_2O_2$ concentration. While a lower concentration (3%–6% HP) is bactericidal, it is only slowly sporicidal, thus needing longer contact times to achieve a satisfactory sporicidal effect. Using higher concentrations (10%–30%) results in faster sporicidal activity in vitro [2, 3, 26].

The mechanism responsible for the antimicrobial effect is DNA strand breakage due to oxidization of the DNA by reactive oxygen species (ROS) that are released by the degradation of HP. ROS are free radicals (molecules with unpaired electrons) that contain oxygen. HP is normally reduced to $H_2O$, but certain metal ions, including iron and titan, can cause free radicals like the highly reactive and tissue damaging hydroxyl radical (·OH) to be formed. Ferrous iron ($Fe^{2+}$) reacts with HP, generating ferric iron ($Fe^{3+}$), the hydroxyl radical (OH), and a hydroxyl ion ($OH^-$) (Fenton reaction). [3, 27, 28].

Mohammadi et al. showed impressive results in graft take of split thickness grafts in patients with chronically colonized burn wounds. After excision and debridement, 2% HP-soaked gauze was applied for 5 min to the study group, while the control group was irrigated with normal saline before grafting. The mean area of vital skin graft after 21 days was significantly higher in chronically colonized burn wounds, which were treated with HP prior to grafting (82.85% versus 65.61% in the control group) [4].

## Hemostasis

Intraoperative control of hemorrhage can be challenging. HP can be used as a chemical hemostasis agent to achieve the desired effect.

Hankin et al. studied the use of HP as a hemostatic agent in adult mongrel dogs after transverse osteotomy of six metaphyseal sites per dog. Blood loss per area per minute was determined before and after treatment of the epiphysis with 3% HP or saline solutions in the control group. Results showed that blood loss was significantly lower for the HP-treated sites than the saline-treated ones. Additionally, after treatment with HP, a mean reduction of 38.7 mg/cm$^2$/min was seen, while treatment with saline solution only showed a mean increase in bleeding of 26 mg/cm$^2$/min [5].

The mechanisms by which hemostasis is achieved are not entirely clear. Mechanisms suggested in the past include thermal injury of vascular ends by exothermal degradation of HP [7], liberation of intimal lipid deposits by ROS [8], oxygen embolization of bleeding vessels [7], development of fibrin thrombi [9], and reactive vascular spasms [8]. Nowadays, it is believed that HP triggers the activation of blood platelets exposed to arachidonic acid and collagen by both stimulating the cyclooxygenase pathway via phospholipase A2 and through the cyclooxygenase independent phospholipase C pathway [6, 10, 11]. The hemostatic effects of hydrogen peroxide can be prevented by either platelet aggregation inhibitors or coexisting catalase [10].

In burn surgery, HP can be used for hemostasis at donor sites as well as at sites of tangential excision. In a case report, Potyondy et al. used HP and electrocauterization to achieve hemostasis in a patient with compromised platelet function after being treated for myocardial infarction, and described good results in terms of hemostasis and an even greater hemostatic effect in this patient than with epinephrine. This group also described the usefulness of HP to locate areas of bleeding with its bubbling effect due to oxygen liberation. A limitation of that particular case report is that the suggested results cannot be objectively measured and the findings are in contradiction with the literature, which proposes the prevention of HP-derived platelet aggregation when treated with acetylsalicylic acid. This discrepancy may need further investigation [6, 10].

## Wound healing

Wound healing is a process that is dynamic and interactive and consists of three phases: inflammation, proliferation, and scar formation [12].

The benefit of HP in wound healing is the subject of controversy. Since the inflammatory stage includes the natural occurrence of HP, one might attribute it to a beneficial effect on wound healing. However, there are studies promoting this theory, while others show an adverse effect of HP on different aspects of wound healing:

### *Inflammation*

Inflammation is the natural response to injury and is characterized by the release of chemotactic factors and vasoactive mediators in order to allow leukocytes, growth factors, enzymes, and antibodies to reach the site of injury. Predominant cells in this phase of healing are neutrophil granulocytes, which release oxidative agents, including HP, to kill foreign pathogens,

but which are also linked to the damage of endogenous cells [13] and macrophages, which phagocytose necrotic and foreign material.

The ability for scarless wound repair of an early fetus is made possible by the absence of inflammation. Wilgus et al. showed that HP can interfere with this scarless healing, likely by inducing TGF-β and fibroblast proliferation, resulting in increased fibrosis of the wound. In their trial, mice fetuses were wounded and treated with 1% HP solution. The wounds were harvested 4 h, 24 h, and 7 days after the intervention for further histological investigation [21].

### *Growth factors*

Growth factors play an important role in wound healing; examples include platelet derived growth factor (PDGF), vascular endothelial growth factor (VEGF), as well as transforming growth factor α and β (TGF-α and TGF-β) [13].

VEGF is, among other things, an HP-induced growth factor, released from macrophages, and is important for angiogenesis and subsequent wound healing. Cho et al. showed that exogenous HP stimulates the release of VEGF in both rat and murine in vitro models in a dose-dependent manner, with a maximal effect seen with 1 mM $H_2O_2$ [14]. Using an HP cream as a topical treatment for ischemic ulcers in guinea pigs resulted in significantly higher vascular perfusion compared to placebo cream, most likely due to increased VEGF activity [22].

Another example of an HP-mediated growth factor is TGF-β. High levels of TGF-β, induced by higher HP concentrations (up to 400 µM in this in vitro study [15]), are linked to a faster healing response, but also to increased proliferation of fibroblasts, which, at high levels, play a role in the formation of pathologic scars [15–17]. While HP in low concentrations (1.5%–3.5%) increases the proliferation of fibroblasts, in vitro experiments showed that high concentrations of HP resulted in cytotoxicity of fibroblast cultures [18].

### *Reepithelialization*

Reepithelialization is a process of epithelium regeneration following tissue loss and requires both the proliferation and the migration of keratinocytes to the edges and bed of the wound. Interference with these mechanisms may lead to delayed wound closure [13]. HP showed a dose-dependent impairment of keratinocyte viability and migration in cell cultures. While concentrations of less than 700 µM (0.02%) showed only little impact on keratinocyte viability, with more than 80% of keratinocytes remaining functional and intact, there was an irreversible reduction in keratinocyte viability and migration seen at concentrations above 2 mM [19].

An in vitro study with alveolar tissue showed that, after acute lung injury, the presence of $H_2O_2$ showed a dose-dependent inhibition of epithelial repair and induction of apoptosis of epithelial cells, especially at the edges of the wound. At a concentration of 200 µM HP, epithelial wound closure within 24 h reduced from 95% to 27%. Apoptosis of the alveolar epithelial cells was suspected to be the mechanism here, resulting in the inhibition of epithelial repair [20].

## Toxicity

There are three mechanisms that account for possible HP toxicity: oxygen gas formation, corrosive damage, and lipid peroxidation [6].

Decomposition of HP can produce substantial volumes of oxygen: 30 ml of 35% HP degrade to a total of 3.5 l of oxygen [23]. If the oxygen partial pressure exceeds the maximal solubility of oxygen in the blood, gas embolisms can occur resulting in, e. g., brain infarction or pulmonary embolism [24]. The release of oxygen in closed body cavities can lead to mechanical tissue damage and even visceral perforation [23]. Ingestion of concentrated HP may require placing a gastric tube to release the gas. The use of 3% HP is not linked to gas embolisms [6].

Concentrated HP (35% [23]) can have a caustic effect on all tissues and result in local damage. Ingestion may lead to irritation of the gastrointestinal tract, ulcers, and bleeding. Inhalation or aspiration due to bubbling in the stomach can lead to subglottic stenosis and laryngospasm and may result in the need for intubation and mechanical ventilation. Ingestion of 3% hydrogen peroxide may cause gastrointestinal irritation and whitening of the mucosa, but these are mostly benign [23, 25].

Ocular exposure may cause stinging, ulceration, and even corneal perforation; the affected eye should be irrigated immediately. Contact with 3% HP solution may lead to irritation and increased lacrimation, but severe impairment is unusual [24].

Concentrated hydrogen peroxide (30%) can cause a cytotoxic effect via lipid peroxidation. However, 3% solutions have not been found to cause this effect [6].

Henry et al. investigated all exposure to 3% HP that were reported to the Long Island Regional Poison Control Center between January 1992 and April 1995. During these 40 months, there were 670 admissions, mostly due to oral ingestion (77%), of which 67% were children. Most patients were asymptomatic (85.6%). All patients, with the exception of one child who developed gastric ulcers and duodenal erosions with persistent hematemesis, showed a benign course [25].

## Conclusions

HP is a useful irrigation solution for both its antiseptic and hemostatic effects. The use of HP to enhance wound healing requires further investigation. While several studies promote beneficial effects in the early

stages of healing, others show inhibitory effects on wound healing in the late stages, which may result in delayed healing and pathological scarring.

The cytotoxic effects of HP via lipid peroxidation and caustic injury appear to be dose-dependent. The degradation of HP causes oxygen gas formation, subsequently leading to possible mechanical tissue damage in closed body cavities and gas embolisms if the partial pressure exceeds the maximal solubility. To minimize these toxic effects of HP via oxygen gas formation, it should not be administered with pressure or to body cavities, but rather as HP-soaked gauze. Although 3% solutions do not appear to have a negative effect on wound healing via cytotoxicity clinically, the irrigation of HP after its use could be useful to prevent tissue damage by high contact times.

In conclusion, a 3% hydrogen peroxide solution is a safe and effective irrigation solution for intraoperative wound cleansing and hemostasis. It can be used in burn surgery to enhance the skin graft take in chronically colonized burn wounds and for hemostasis of both donor sites and sites of tangential excision. It can also be administered to chronic wounds for its antimicrobial effect and beneficial effect on healing via neoangiogenesis. It may be used as a topical agent to shorten healing time and promote early separation of the wound scab, but should not be administered once reepithelialization is in progress, since it may have adverse effects on the new epithelium.

**Conflict of interest** M.V. Urban, T. Rath, and C. Radtke declare that they have no competing interests.

## References


1. Marshall MV, Cancro LP, Fischman SL. Hydrogen peroxide: a review of its use in dentistry. J Peridontol. 1995;66(9):786–96.
2. Drosou A, Falabella A, Kirsner RS. Antiseptics on wounds: an area of controversy. Wounds. 2013;15(5):149–66.
3. McDonnell G, Russel AD. Antiseptics and disinfectants: activity, action, and resistance. Clin Microbiol Rev. 1999;12(1):147–79.
4. Mohammadi AA, Seyed Jafari SM, Kiasat M, Pakyari MR, Ahrari I. Efficacy of debridement and wound cleansing with 2 % hydrogen peroxide on graft take in the chronic-colonized burn wounds; a randomized controlled clinical trial. Burns. 2013;39:1131–6.
5. Hankin FM, Campbell SE, Goldstein SA, Matthews LS. Hydrogen peroxide as a topical hemostatic agent. Clin Orthop Relat Res. 1984;186:244–8.
6. Potyondy L, Lottenberg L, Anderson J, Mozingo DW. The use of hydrogen peroxide for achieving dermal hemostasis after burn excision in a patient with platelet dysfunction. J Burn Care Res. 2006;27(1):99–101.
7. Schumb WC, Satterfield CN, Wentworth RL. Hydrogen peroxide. New York: Reinhold Publishing Corp; 1955. pp. 5–21.
8. Urschel H, McNamara J, Aslami A. Effects of hydrogen peroxide on arteriosclerosis. Surgery. 1968;63:21.
9. Jacques LB, Bell HJ. The reduction of hydrogen peroxide by fibrin. Can J Res. 1946;24:79–83.
10. Pratico D, Iuliano L, Ghiselli A, Alessandri C, Violi F. Hydrogen peroxide as trigger of platelet aggregation. Hemostasis. 1991;21(3):169–74.
11. Pratico D, Iuliano L, Pulcinelli FM, Bonavita MS, Gazzaniga PP, Violi F. Hydrogen peroxide triggers activation of human platelets selectively exposed to nonaggregating concentrations of arachidonic acid and collagen. J Lab Clin Med. 1992;119(4):364–70.
12. Singer AJ, Clark RA. Cutaneous wound healing. N Engl J Med. 1999;341:738–46.
13. Wasserbauer S, Perez-Meza D, Chao R. Hydrogen peroxide and wound healing: a theoretical and practical review for hair transplant surgeons. Dermatol Surg. 2008;34:745–50.
14. Cho M, Hunt TK, Hussain MZ. Hydrogen peroxide stimulates macrophage vascular endothelial growth factor release. Am J Physiol Heart Circ Physiol. 2001;280:H2357–H63.
15. Barcellos-Hoff MH, Dix TA. Redox-mediated activation of latent transforming growth factor-beta 1. Mol Endocrinol. 1996;10(9):1077–83.
16. Park SK, Kim J, Seomun Y, Choi J, Kim DH, Han IO, Lee EH, Chung SK, Joo CK. Hydrogen peroxide is a novel inducer of connective tissue growth factor. Biochem Biophys Res Commun. 2001;284(4):966–71.
17. Garcia-Trevijano ER, Iraburu MJ, Fontana L, Domínguez-Rosales JA, Auster A, Covarrubias-Pinedo A, Rojkind M. Transforming growth factor beta 1 induces the expression of alpha 1(I) procollagen mRNA by a hydrogen peroxide-C/EBPbeta-dependent mechanism in rat hepatic stellate cells. Hepatology. 1999;29:960.
18. Chung LY, Schmidt RJ, Andrews AM, Turner TD. A study of hydrogen peroxide generation by, and antioxidant activity of, Granuflex hydrocolloid granules and some other hydrogel/hydrocolloid wound management materials. Br J Dermatol. 1993;129:145–53.
19. O'Toole EA, Goel M, Woodley DT. Hydrogen peroxide inhibits human keratinocyte migration. Dermatol Surg. 1996;22:525–9.
20. Geiser T, Ishigaki M, van Leer C, Matthay MA, Broaddus VC. H2O2 inhibits alveolar epithelial wound repair in vitro by induction of apoptosis. Am J Physiol Lung Cell Mol Physiol. 2004;287:L448–L53.
21. Wilgus TA, Bergdall VK, Dipietro LA, Oberyszyn TM. Hydrogen peroxide disrupts scarless fetal wound repair. Wound Repair Regen. 2005;13:513–9.
22. Tur E, Bolton L, Constantine BE. Topical hydrogen peroxide treatment of ischemic ulcers in the guinea pig: blood recruitment in multiple skin sites. J Am Acad Dermatol. 1995;33(1):217–21.
23. Pritchett S, Green D, Rossos P. Accidental ingestion of 35 % hydrogen peroxide. Can J Gastroenterol. 2007;21(10):665–7.
24. Watt BE, Proudfoot AT, Vale JA. Hydrogen peroxide poisoning. Toxicol Rev. 2004;23(1):51–7.
25. Henry MC, Wheeler J, Mofenson HC, Caraccio TR, Marsh M, Comer GM, Singer AJ. Hydrogen peroxide 3 % exposures. J Toxicol Clin Toxicol. 1996;34(3):323–7.
26. Russell AD. Bacterial spores and chemical sporicidal agents. Clin Microbiol Rev. 1990;3(2):99–119.
27. Jaimes EA, Sweeney C, Raij L. Effects of the reactive oxygen species hydrogen peroxide and hypochlorite on endothelial nitric oxide production. Hypertension. 2001;38:877–83.
28. Krötz F, Sohn HY, Pohl U. Reactive oxygen species: players in the platelet game. Arterioscler Thromb Vasc Biol. 2004;24:1988–96.