



Original Article

Histopathological changes of neuronal tissue following the use of hydrogen peroxide in neurosurgical procedures

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Received : 21 January 2020

Accepted : 17 January 2021

Published : 08 March 2021

DOI

10.25259/SNI_26_2020

Quick Response Code:



ABSTRACT

Background: Hydrogen peroxide (HP) is routinely used in neurosurgical procedures to achieve surgical hemostasis. However, its safety profile is still debatable with various reports depicting range of adverse effects on neuronal tissue. The objective of this paper is to evaluate the safety and efficacy of HP as a hemostatic agent in normal neuronal tissue during neurosurgical procedures conducted on rats.

Methods: One hundred rats were divided into three groups. The first and third group underwent cortical irrigation with HP and the second group underwent spinal irrigation with HP. All groups were irrigated with different concentrations of HP (1%, 3%, or 6%) for 3 min and tissue biopsies were obtained immediately afterwards (Groups A and B) or 1 week after HP irrigation (Group C). Study specimens were examined histologically and compared to control tissue.

Results: All rats showed normal behavioral, functional, and motor neurological activity following the procedures. Histopathologically, dark neurons were observed in all HP exposed tissue. The cytoplasm revealed condensed and dark Nissl substance and the neurites and axons exhibited a corkscrew morphology. No ischemic changes or inflammatory infiltrates were detected. The majority of dark neurons were observed at the periphery of tissue fragments. These findings were present and consistent in both the short- and long-term groups.

Conclusion: HP irrigation showed no significant short- or long-term clinical and histopathological changes in comparison to normal saline when used on rats' neuronal tissue. This may confirm the safety of intraoperative HP usage as hemostatic agent during neurosurgical procedures.

Keywords: Brain, Hemostasis, Hydrogen peroxide, Intracerebral hemorrhage, Spinal cord

INTRODUCTION

Achieving hemostasis in neurosurgery is considered a key element to prevent postoperative complications and the need for reoperation. Various methods have been utilized to achieve this goal including thermal, mechanical, and chemical hemostasis.^[1] As a chemical method for hemostasis, hydrogen peroxide (HP) solution has been widely utilized in cranial and spinal

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procedures.^[5,14,15] Its use in other surgical specialties has been extensively reported as well due to its antimicrobial and hemostatic properties.^[6,7,10]

Although the use of HP results in favorable hemostatic outcomes, its potential deleterious effects on neuronal tissue is not fully investigated. The objective of this study was to evaluate the safety and efficacy of HP as a hemostatic agent in neurosurgical procedures by examining the clinical and histopathological changes of normal rats' neuronal tissue following the exposure to different HP concentrations.

MATERIALS AND METHODS

All animal procedures were approved by King Saud University College of Medicine Animal Care and Use Committee and the Institutional Review Board Committee at King Fahad Medical City (Riyadh, Saudi Arabia). A total of 100 male Wistar albino rats weighing 250 g–300 g were obtained and divided into three groups (Groups A, B, and C). Rats' age, sex, species, and weight were similar among the groups. Group A included 60 rats and was further subdivided into three groups with 20 rats each. Group B included 30 rats and was further subdivided into three groups with ten rats each. Group C included ten rats and was further subdivided into two groups with five rats each [Figure 1].

Each animal was anesthetized using pentobarbitone (50 mg/kg body weight) before the neurosurgical procedure. Rats in Groups A and C underwent cranial procedures while those in Group B underwent spinal procedures. Groups A and B rats received irrigation with normal saline (control specimen) and one of three (1%, 3%, or 6%) HP concentrations (study specimen) for 3 min [Figure 1]. Immediately after the irrigation, we took tissue biopsies from the brain (Group A) or spinal cord (Group B), which were examined histologically and compared with control specimens. Group C received an intracranial irrigation of HP with 1 week follow-up to evaluate the long-term effects of HP.

Rats in Group C underwent craniotomy and were irrigated with 5 mL HP (3% and 6%). They were monitored for 1 week before taking the brain tissue samples.

Control tissue was obtained from the same rat with either interhemispheric brain or interdistal spinal cord tissue following irrigation with normal saline for 3 min. Group C animals were monitored and clinically assessed for any neurological change for 1 week following the use of HP.

Cranial procedures

Skulls of Group A rats were exposed using a longitudinal incision in the midline after an infiltration with 2% lidocaine with epinephrine; a right unilateral craniotomy was then performed using a manual drill (Stoelting Co., IL). The dura was then opened with a number ten blade scalpel. A small corticectomy was performed and the exposed brain tissue was irrigated with 0.9% normal saline for 3 min, and a control brain specimen was obtained and placed in 10% formalin for fixation. Another craniotomy on the left side was performed in the same fashion as the right side. A small corticectomy was performed and the brain tissue was irrigated with one of three HP concentrations (1%, 3%, or 6%) for 3 min followed by irrigation with normal saline and suctioning. Study specimens were collected from the irrigated area. Animals were sacrificed immediately thereafter with an overdose of pentobarbital.

Spinal procedures

The spine was exposed using a longitudinal incision in the midline and laminectomies were performed in two non-contiguous levels (upper cervical and lower thoracic). Cottonoid at the caudal end of the cervical laminectomies and at the rostral end of the lower thoracic laminectomies were placed to avoid contamination and cross spillage. A small incision in the spinal cord was made in both areas and the upper levels were irrigated with normal saline for

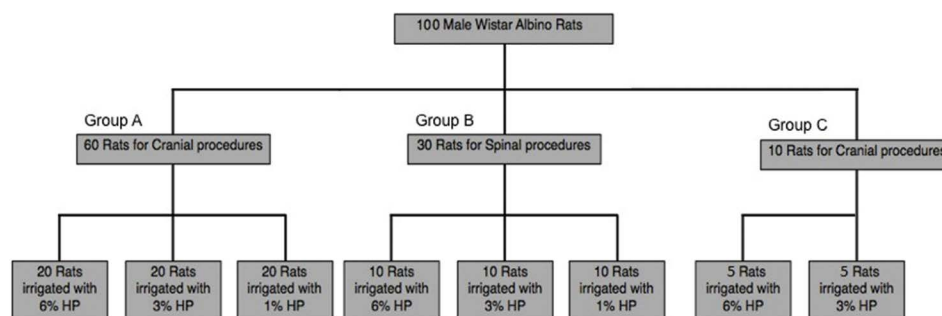


Figure 1: Distribution of the different concentration of hydrogen peroxide (HP) among the experimental groups. Group A ($n = 60$) underwent cranial procedures and received irrigation of 1%, 3%, and 6% HP. Group B ($n = 30$) underwent spinal procedures and received irrigation of 1%, 3%, and 6% HP. Group C ($n = 10$) received an intracranial irrigation of 3% and 6% HP and was sampled after 1 week to evaluate the long-term effects of HP.

3 min, while the lower levels were irrigated with one of three HP concentrations (1%, 3%, or 6%) for 3 min followed by irrigation with normal saline and suctioning. Spinal cord tissue and dura specimens were collected from the exposed upper levels (control specimen) and lower levels (HP specimen). Animals were sacrificed immediately thereafter with an overdose of pentobarbital.

Cranial procedures for long-term effect

The rats in Group C were positioned in a stereotaxic frame (Stoelting Co., IL). In a sterile field, a midline scalp incision was made, and the underlying muscles were removed. A unilateral burr hole was drilled. A 10 μ l Hamilton microsyringe was used to irrigate 3% or 6% HP. The syringe was mounted on a syringe holder and fixed on the stereotaxic frame. The needle was lowered to exactly 5.0 mm below the surface of the skull. A volume of 5 μ l of 3% or 6% HP according to the subgroup was irrigated slowly at a rate of 1 μ l/min. The needle was slowly removed to prevent the injected fluid from escaping the needle tract. All rats received prophylactic antibiotics. The skin incision was sutured using 3–0 silk suture. The rats were kept under observation for 1 week. After 1 week, the rats were anesthetized in a similar fashion as described previously. The first burr hole was opened, and a study specimen was obtained. Adjacent to the site of the first hole, another burr hole was made, and control brain tissue was obtained and stored in 10% buffered formalin for evaluation. Animals were sacrificed immediately thereafter with an overdose of pentobarbital.

Tissue sampling and processing

Two hundred samples were sent to an independent neuropathologist for evaluation. Perfusion, tissue removal, fixation, sectioning, and mounting on glass slides were performed as previously described.^[29] Briefly, control and study specimens from the brain and spinal cord tissues were fixed with formalin and transferred to the Department of Pathology and Laboratory Medicine at King Fahad Medical City. Tissue was embedded in paraffin, sectioned at a thickness of 5 μ m, and stained with hematoxylin and eosin for histological evaluation under different magnifications. Slides were examined for evidence of injury or degeneration. Specimens exposed to HP were examined histologically and compared with control samples. Dark neurons were quantified using incremental percentages (25%, 50%, 75%, and 100%).

Statistical analysis

Statistical analysis was performed using one-way ANOVA and Duncan's method for pairwise multiple comparisons. Data are expressed as the mean \pm SEM. Statistical analysis

was performed using SPSS version 17.0 (IBM Corporation, USA).

RESULTS

Clinical outcomes

During the 1-week monitoring of Group C rats, all animals showed normal behavioral, functional, and motor neurological activity with no neurological deficits following HP application.

Histopathological findings

Across both cranial and spinal specimens, the cytoplasm revealed condensed and dark Nissl substance. The neurites and axons exhibited corkscrew morphology [Figures 2 and 3] and were easily discernible from the adjacent normal neurons. There were no ischemic changes or inflammatory infiltrates. Neither single cell necrosis (red neurons) nor diffuse necrosis was observed. The majority of dark neurons were observed at the periphery of tissue fragments. These features were observed among all study specimens. Three samples (two from the rats exposed to 1% HP and one from the rats exposed to 6% HP), however, demonstrated focal mild lymphohistiocytic aggregates.

The dark neurons were present in nearly equal percentages in the experimental and control tissues [Tables 1 and 2]. There was no statistically significant difference in the percentage of dark neurons between the control tissue and the HP-treated tissue in all groups. Furthermore, different HP concentrations (1%, 3%, or 6%) failed to demonstrate immediate and long-term statistically significant difference in the occurrence of dark neurons. The histopathological changes of brain tissue were comparable with spinal cord tissue changes exposed to different concentrations of HP in Groups A and B. For long-term results, Group C rats demonstrated similar results to the other groups 1 week after HP application, with no signs of ischemia, inflammation, or necrosis.

DISCUSSION

HP is routinely utilized during cranial and spinal cord surgeries to achieve hemostasis.^[5,14,19] The resultant exothermic chemical reaction is attributed to the generated reactive oxygen species released during its contact with the tissues (10 mL of oxygen for 1 mL of 3% HP).^[19] Although the exact mechanism remains not well understood, HP's hemostatic property is thought to be related to induced vasoconstriction, platelet aggregation, thrombus formation, and small blood vessel microbubbles occlusion.^[4,15–17]

Despite its evident efficacy, HP safety remains debatable. To the best of our knowledge, HP's safety has been evaluated in

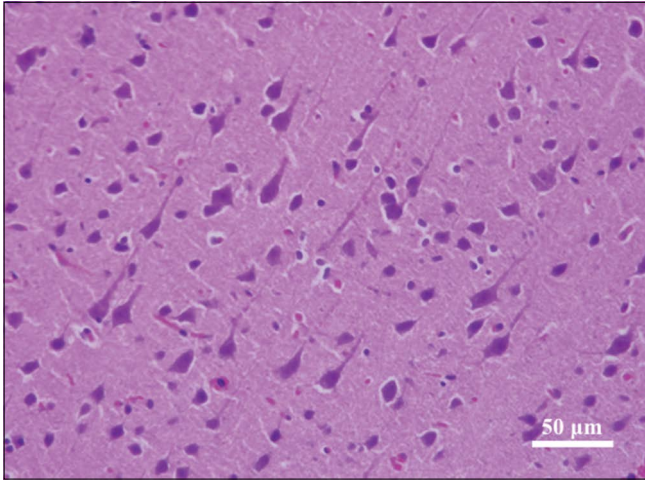


Figure 2: Hematoxylin and eosin microscopic evaluation, under a magnification of $\times 40$, of excised brain tissue after applying 1% hydrogen peroxide, which yielded dark neurons (although not presented, spine samples showed similar findings).

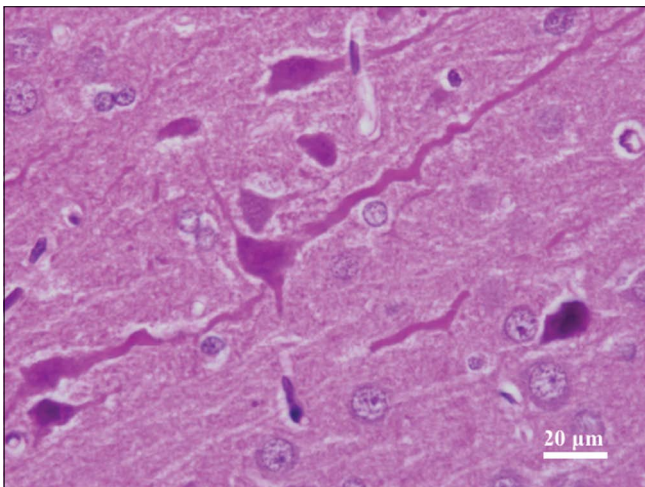


Figure 3: Hematoxylin and eosin microscopic evaluation, under a magnification of $\times 100$, of excised spine tissue after applying 3% hydrogen peroxide, depicting the neurites and axons of dark neurons exhibiting a corkscrew morphology (although not presented, brain samples showed similar findings).

at least six studies, in which histopathological changes were assessed following the use of HP on neural tissue.^[8,15,21,26-28] Hansson and Vallfors^[8] studied the effects of applying 3% HP *in vitro* on newborn rat brain cells compared to other irrigation fluids. They observed that the number of cells was drastically decreased after 10 s of incubation with evident cell death after 5 min of incubation, which was not observed with the other solutions, including normal saline. Similarly, Vallfors *et al.*^[27] conducted an *in vivo* study where they applied 3% HP on cat brain tissue. The authors found thrombosis of the leptomeningeal vessels and extensive dysfunction of the blood-brain barrier from the cortex to the white matter. In

addition, using scanning electron microscopy, they reported complete meningeal cell disintegration of the subdural and arachnoid surfaces after 5 min of exposure to HP with preservation of the collagenous connective tissue.^[26] The meningeal cell integrity was also violated in some samples when other irrigation fluids were utilized, however, to a lesser degree of disintegration. Therefore, concerns regarding the safety of HP in neurosurgical procedures were raised.

On the contrary, none of the aforementioned changes were evident in the rats' brain and spinal cord tissue in our study. In all 100 rats, only dark neurons could be observed in both experimental and control groups with no statistically significant difference between the three groups, or between the cranial and spinal groups. The histopathological changes were similar in the short-term groups (A and B) and long-term group (C) with no signs of ischemia, inflammation, or necrosis in all groups. The prevalence of dark neurons at the periphery of the tissue can be attributed to the strong and rapid formaldehyde penetration at the edge of the tissue or to the death of neurons in the center of the examined specimen, which precludes the formation of dark neurons. In addition, the prevalence of dark neurons might be attributed to the difference in exposure time between our study and the reported studies (3 min vs. 5 min), which may affect the occurrence of neuronal cell death, the different species (rats vs. cats) studied, or the histopathological interpretation of dark neurons. Although our findings are inconsistent with the results of previous studies, they are consistent with the ongoing clinical practice and observed patients' outcomes.

Various *in vitro* studies have also observed tumoricidal activity of HP on different types of cancer cells.^[15,18] Mesiwala *et al.*^[15] compared the tumoricidal effects of varied concentrations of HP (0–30%) and ethanol (0–50%) on human brain surgical specimens and rat tumor cell lines. Although both HP and ethanol demonstrated similar concentration-dependent tumoricidal effects *in vitro*, HP led to a more significant injury to the arachnoid and stroma with evident neuronal and glial injury. Similarly, Kwon *et al.*^[11] studied the changes of astrocytoma cell lines incubated with different concentrations of HP. Their analysis showed that HP upregulated Fas/FasL expression in astrocytoma cell lines leading to their enhanced apoptosis and tumor cell death.

In addition to its hemostatic and antitumor activities, HP is a potent oxidizing reagent and thus, it is commonly used to disinfect wounds against a wide range of microorganisms. As HP contacts tissues, it generates reactive oxygen species such as singlet oxygen and hydroxyl radicals that react with membrane lipids and bacterial DNA.^[24,25] Various studies have shown that intraoperative usage of HP resulted in significant reduction of intervertebral space infection from 1.5–2.8% to 0–0.4%.^[2,25]

Table 1: A comparison of the subgroups of Group A in which Groups I, III, and V were compared with Groups II, IV, and VI, respectively. No statistically significant differences were observed between experimental and control groups.

Subgroups	n	HP, %	NS, %	Dark neurons, %				P-value
				25	50	75	100	
Group I	20	1	-	7	8	2	3	> 0.1
Group II	20	-	0.9	10	6	2	2	
Group III	20	3	-	9	6	3	2	
Group IV	20	-	0.9	7	9	3	1	
Group V	20	6	-	7	9	1	3	
Group VI	20	-	0.9	9	8	1	2	
Total	120			49	46	12	13	
				120				

HP: Hydrogen peroxide, NS: Normal saline

Table 2: A comparison of the subgroups of Group B in which Groups I, III, and V were compared with Groups II, IV, and VI, respectively. No statistically significant differences were observed between experimental and control groups.

Subgroups	n	HP, %	NS, %	Dark neurons, %				P-value
				25	50	75	100	
Group I	10	1	-	5	4	1	0	>0.1
Group II	10	-	0.9	4	3	2	1	
Group III	10	3	-	3	5	1	1	
Group IV	10	-	0.9	4	5	0	1	
Group V	10	6	-	4	4	2	0	
Group VI	10	-	0.9	5	3	2	0	
Total	60			25	24	8	3	
				60				

HP: Hydrogen peroxide, NS: Normal saline

In clinical settings, Lichtenbaum *et al.*^[12] were the first to report the use of HP as an adjunct during the resection of meningiomas. This direct intratumoral HP injection technique enabled them to resect meningiomas without the need for preoperative embolization. Although no complications were reported in their cohort, several studies reported various complications associated with HP use especially during sellar, posterior fossa, and cervical spine surgeries.^[4,16,22] These adverse effects included cardiovascular instability, venous gas embolism, and pneumocephalus, among others.^[19,20,30] These complications may occur when HP diffuses into the ventricles or is applied directly in them as it decomposes into water and oxygen by exposure to a variety of catalase enzymes.

Oxygen embolization is the most commonly reported complication associated with HP use with less than 10 cases reported in the literature.^[3,4,9,13,19] However, the results of two of these cases are questionable as these patients were operated on a sitting position, which is a well-known risk factor for oxygen embolization by itself. Morikawa *et al.*^[16] reported a case of oxygen embolism associated with HP irrigation during cervical spinal surgery. Although their case went uneventful, they discouraged the use of HP due

to its potential hazards related to venous embolism and hemodynamic instability. Similarly, Spiriev *et al.*^[23] reported a case of large chronic subdural hematoma evacuation where a transient trigemino-cardiac reflex (hypotension and bradycardia) occurred on irrigating the hematoma cavity with 3% diluted HP and applying HP-soaked gauzes in the cavity. After the gauzes were removed and the cavity was irrigated with normal saline, hemodynamic parameters returned to normal and remained stable. Based on this, they recommended avoiding the use of HP during intracranial procedures, especially near eloquent areas and trigeminally innervated intracranial structures. Therefore, caution should be taken whenever HP is applied, and instant irrigation with normal saline and removal is essential if a complication is encountered.

Limitations

Our study is limited by the lack of assessment of meningeothelial cells, leptomeningeal vasculature, and blood-brain barrier changes following HP application as well as the lack of other measures in assessing neuronal response such as immunofluorescence testing and immunohistochemical and nuclear stains. We did not

perform an extensive histopathological examination to the wounded surfaces as well. In addition, the study is limited by the lack of standardized measurements of behavioral, functional, and motor neurological activity of the rats in prolonged application group (Group C). However, our study demonstrates that HP safety is comparable to that of normal saline when applied carefully to the brain and spinal cord surfaces.

CONCLUSION

Intraoperative usage of HP is potentially safe and effective modality to achieve hemostasis in neurosurgical procedures. Our study demonstrated the absence of significant short- and long-term clinical and histopathological changes following HP application in comparison to normal saline in rats' brain and spinal cord tissue.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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How to cite this article: Alshardan MM, Abunimer AM, Abou-Al-Shaar H, Aldandan S, El-Watidy SM, Mustafa AM, *et al.* Histopathological changes of neuronal tissue following the use of hydrogen peroxide in neurosurgical procedures. *Surg Neurol Int* 2021;12:91.