

Medical management of paraquat induced oral mucositis: A systematic Review

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Abstract

Paraquat is an extremely corrosive and lethal herbicide. After intentional or unintentional ingestion, paraquat causes extensive mucosal damages extending through the upper gastrointestinal tract which are characterized by pain, inflammation, ulceration, bleeding, and sloughing of the associated mucosa. The aim of this systematic review is to compile and evaluate evidence based studies in relation to the effectiveness of different methods of management of oral mucositis induced by paraquat in terms of reduction of associated pain and duration of symptoms. We undertook computerized electronic searches through both English and Chinese databases so as to identify all published articles in the subject. We also searched reference lists from relevant articles for any related articles. This review is not registered. A total of 10 relevant randomized controlled trials (RCTS) were selected after the electronic searches after satisfying our inclusion criteria. They were published between the 2000s and 2020. The primary outcome measurement assessed an improvement in the healing time/recovery time or adequate pain management. Interventions from all the studies highlighted the use of multi-agent management that included either oral care by the use of bland and multi-agent mouth rinses, corticosteroids, Chinese herbal remedies, growth factors, smectites or anti-oxidant therapy. The main findings were that the main method of management was the implementation of a multi-drug regimen, through the use of compounded preparations or a polydrug system. In addition, herbal and natural remedies, if used appropriately, can play a beneficial role in the management of paraquat induced oral mucositis.

Title

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Running title

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What is already known

Paraquat causes extensive mucosal damages by pain, inflammation, ulceration, bleeding, and sloughing of the associated mucosa.

There are fabulous ways of oral care, however, a use of compounded preparations or a polydrug system has not been reviewed yet.

What this paper adds

This review found that the main method of management was the implementation of a multi-drug regimen, through the use of compounded preparations or a polydrug system.

Herbal and natural remedies may play a beneficial role in the management of paraquat induced oral mucositis.

Abstract

Paraquat is an extremely corrosive and lethal herbicide. After intentional or unintentional ingestion, paraquat causes extensive mucosal damages extending through the upper gastrointestinal tract which are characterized by pain, inflammation, ulceration, bleeding, and sloughing of the associated mucosa. The aim of this systematic review is to compile and evaluate evidence based studies in relation to the effectiveness of different methods of management of oral mucositis induced by paraquat in terms of reduction of associated pain and duration of symptoms. We undertook computerized electronic searches through both English and Chinese databases so as to identify all published articles in the subject. We also searched reference lists from relevant articles for any related articles. This review is not registered. A total of 10 relevant randomized controlled trials (RCTS) were selected after the electronic searches after satisfying our inclusion criteria. They were published between the 2000s and 2020. The primary outcome measurement assessed an improvement in the healing time/recovery time or adequate pain management. Interventions from all the studies highlighted the use of multi-agent management that included either oral care by the use of bland and multi-agent mouth rinses, corticosteroids, Chinese herbal remedies, growth factors, smectites or anti-oxidant therapy. The main findings were that the main method of management was the implementation of a multi-drug regimen, through

the use of compounded preparations or a polydrug system. In addition, herbal and natural remedies, if used appropriately, can play a beneficial role in the management of paraquat induced oral mucositis.

Background

Paraquat, which also has the chemical name 1,10 -dimethyl-4,40 -bipyridinium dichloride, is an organic heterocyclic contact herbicide that is widely used in agriculture for weed and grass control throughout the world and especially in China. The main toxokinetic mechanism of paraquat toxicity involve the formation of superoxide anions during the 'redox cycling process' which then leads to the formation of toxic reactive oxygen species such as hydrogen peroxide and hydroxyl radical in the presence of NADPH and cytochrome P450 reductase.^{1 2 3} The accumulation of reactive oxygen species leads to cell death in different organs. The clinical complications that arise from paraquat poisoning are; acute renal failure, liver toxicity, respiratory failure, and mucosal injury.^{4 5} Early mortality can occur within 1–4 days due to multiple organ failure, while delayed mortality can occur after as long as 3 weeks as a result of respiratory failure secondary to pulmonary fibrosis. The prognosis of paraquat poisoning is poor, and this is elicited by its high mortality rate of 36-90%.^{6 7}

Oral ingestion of paraquat is accompanied by severe oral mucosal injuries (ulcerations of the oral mucosa and the tongue) and corrosive esophageal injuries. Paraquat exposure leads to the over accumulation of reactive oxygen species and oxidative stress exerted to the mucosa.^{8 9} The body produces a strong emergency response by the production pro-inflammatory cytokines and stress responders. This amplified response causes a cycle of constant production of cytokines that result in further damage and ulceration of the mucosa.¹⁰ The early manifestations of mucosal injury are erythema, congestion and edema of the mucosa, which then progresses to erosion, inflammation, ulceration, coating, bleeding, and sloughing of the oropharyngeal mucosa. These changes are observable within hours to several days after the ingestion of paraquat.^{11 12}

Patients with oral mucosal injury experience unbearable pain that most describe as a severe burning sensation. The pain associated with paraquat induced mucosal injury significantly compromises nutritional intake, mouth care, and quality of life. The severity of mucosal injury can also be exacerbated by local factors, such as trauma from overzealous oral hygiene, improper nutrition or microbial colonization leading to infections. Infections associated with mucosal injury not only increases the intensity of pain experienced by the patients but may also end up causing life threatening systemic sepsis.¹³ Decreased nutritional intake also lead caloric deficits that compromise the patients nutritional status, reduce treatment response, increase treatment complications, and further elongate hospital stays.

Literature concerning paraquat induced mucosal injury is sparse and not detailed. Through this systematic review, we hope to evaluate and highlight the correct techniques to achieve proper oral care, nutritional support and possible clinical-therapeutic interventions that have proven to be effective in managing paraquat mucosal injuries, with the aim of reducing patient discomfort and overall improving the patients' quality of life.

Description of pathogenesis of paraquat induced mucosal injury

Paraquat, as all bipyridyl salts, is caustic in nature. After ingestion, the local corrosive effects of paraquat cause erythema, irritation to the oral and gastrointestinal mucosa; this further worsens to ulceration and sloughing of the mucosa. The cellular effects of paraquat are exerted due to redox cycling leading to the formation of reactive oxygen species, whose concentration increases significantly in time, which can lead to a situation described as oxidative stress. This phenomenon occurs when there is an overproduction of reactive oxygen species, the high overwhelm the natural radical blocking or scavenging mechanisms of the existing antioxidant defense systems. This intracellular oxidative stress is generated by accumulation of superoxide anion, hydrogen peroxide, and hydroxyl radicals within the cells. Destructive actions of reactive oxygen

species on the cells include: free radical-mediated lipid oxidation leading to production of phospholipid peroxides, oxidative damage of proteins, carbohydrates and nucleic acids.^{8 9}. The effects eventually lead to the subsequent disruption of cellular metabolism, apoptosis and finally programmed cell death. These effects eventually cause epithelial thinning and mucosal damage. Therefore, this oxidative stress process also plays a key role in the associated subsequent mucosal (oral and gastrointestinal) damage caused by paraquat. Another complication that arises from the over accumulation of reactive oxygen species is inflammation. This activate transcription factors which results in upregulation of pro-inflammatory cytokines, cytokines modulators, adhesion molecules, and stress responders. This amplification causes a cycle of constant production of cytokines that result in further damage and ulceration of the mucosa and increases pain and discomfort.^{10 14}

Another precipitating factor in the extent and severity of oral mucosal injury is microbial colonization of the ulcers and the damaged mucosa. The oral cavity is coated by a plethora of bacteria, and some of these bacteria are harmful and are implicated in oral diseases (caries and periodontitis) and several systemic diseases.¹³ Most ulcers are covered by a whitish pseudomembrane composed of dead cells and fibrin. The pseudomembrane creates a favorable environment for bacterial colonization by both Gram-positive and Gram-negative organisms. Secondary infections caused by the bacteria and by-products of bacterial metabolism further intensifies mucosal inflammation, leading to further damage.¹⁵ **Figure 1**

Methods

Literature search

We performed a detailed systematic search through both medical and nursing databases (PUBMED (MEDLINE), SCOPUS, SCIENCE DIRECT, EBSCO, CNKI, XUESHU and COCHRANE DATABASE) to identify related clinical trials in relation to mucosal damaged induced by paraquat between 2000 to December 2020. Our searches explored the keywords (paraquat, paraquat induced oral mucositis, paraquat tongue, oral care, mucosal injury). The population, intervention, comparison, outcome (PICO) model was used to develop inclusion criteria and search terms per intervention. Population focused on patients who presented with symptoms of oral mucositis after paraquat ingestion. Intervention highlighted the different agents and modes of intervention that were applied in the different trials and a comparison of the management received by the control group and a lack thereof. Outcome was based on improved healing/recovery time.

Eligibility criteria

Inclusion criteria

1. Clinical trials
2. English articles or articles with English abstracts
3. Studies from the beginning of the year 2000 to the end of 2020.

Exclusion criteria

1. Case reports
2. Review of literatures
3. Clinical trials published entirely in other languages
4. Animal studies
5. In-vitro studies

Both two authors searched for articles that met selection criteria. The articles that did not meet the selection criteria and duplicate articles were removed from the study. Both two authors then screened the remaining papers individually to confirm their eligibility.

Data collection

Two author's independently extracted data using the standard data extraction form that highlighted; The author's information, year of study, study design, treatment modality used in paraquat induced oral mucositis, route of administration of agent , interventions and outcomes.

Risk of bias assessment across individual studies

Each study was assessed for risk of bias by two review authors independently. The Cochrane Collaboration's tool for assessing risk of bias comprises a description and a judgment for the following criteria: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other sources of bias. Each criterion was judged 'low risk of bias', 'high risk of bias', or 'unclear risk of bias'. This review is not registered.

Ethics approval and consent to participate

Not applicable.

Results

According to the search strategy a total of 116 studies were recognized. According to the inclusion and exclusion criteria, ten articles were finally included after manual screening and evaluation. All the included studies were randomized controlled trials. **Figure 2** shows that the initial computerized search strategy that yielded the 10 included studies. **Table 1** presents a brief description of the 10 articles analyzed in terms of treatment population, intervention applied and comparison and the overall outcome. All the 10 studies showed significant result in terms of improvement on the healing time/recovery time and pain reduction. Results for each intervention are discussed briefly below and should be read in concert with the details shown in **Table 2** . In general, although all of the included studies mentioned the randomized allocation of participants, none of the trials described the methods of sequence generation, allocation concealment, and blinding. As previously mentioned, the risk of bias of individual studies was independently assessed by both two authors using the Cochrane Risk of Bias assessment tool. The findings were shown on

Figure 3.

Highlights on the reviewed interventions

Oral care

Maintenance of oral hygiene and proper oral decontamination play a major role in the management of patients who present with mucosal injuries. Microbial colonization of the oral cavity exacerbates the severity of tissue damage and increases the risk of localized and disseminated infections. Therefore decontamination may help to reduce the probability of further complications like secondary infections that may disseminate into systemic sepsis and also an increase in associated pain. The basic components of an oral care protocol include assessment, patient education, tooth brushing and bland oral rinses (normal saline and sodium bicarbonate). Oral assessment should be conducted regularly to assess function in terms of ability to feed normally, pain, and the extent of damage to the oral mucosa. Although oral care has cannot prevent the formation of paraquat induced oral mucositis, adherence to a regimen can reduce the duration and severity of mucositis. Three studies have demonstrated the superiority of using proper oral care after paraquat ingestion.^{16 1718} All the three studies showed a significant decrease in the severity of symptoms and an improvement in the recovery time.

The first study emphasized the need of early implementation of oral care in patients with history of paraquat ingestion despite the presence or lack thereof oral mucosal lesions.¹⁶ The treatment group received proper oral care at presentation and the control group received oral care three days after ingestion of paraquat. The study showed that early oral care at presentation not only reduced the severity of pain but also decreased the severity of oral mucositis

Bland oral rinses also play an important role in oral care and oral decontamination; alternatively bland oral rinses can also be used in combination with other drugs for the preparation of compounded mouth washes.^{19 20 21 22 23} Normal saline and sodium bicarbonate not only aid in the removal of paraquat residue that may be present in the oral cavity after ingestion but also ensure the removal of oral debris like food particles, therefore preventing the possibility of secondary infections and therefore promoting fast wound healing. Bland rinses also ensure that the oral cavity is adequately moisturized, therefore prevent crusting and thus soothing gums and mouth mucosa therefore increasing patients' comfort.^{16 17 18}

Oral assessment also plays an important role in evaluating whether the patients can normally brush their teeth. After assessment, brushing should be withheld in patients with extensive mucosal injury. Patients with minimal or localized oral mucosal injury should use soft bristle brushes and ensure that they brush their teeth gently. Tooth brushing should be encouraged 2 to 3 times a day or basically after every meal.^{18 24}

Multi-agent or compounded preparations

Multi-agent formulations contain several ingredients (at least three ingredients). These ingredients may include an antibiotic, a local anesthetic or topical anesthetic and a steroid to reduce inflammation. Most formulations are used every 4-6 hours. Patients are advised to hold the formulation in the mouth for 2-5 minutes, then spit out or swallow, and to abstain from eating or drinking for 30 minutes after use. The three studies that focused on multi-agent preparations and mouthwashes have not only demonstrated their superiority over bland rinses to treat mucositis but also alleviate pain.^{21 22 25}

Topical anesthetics (Lidocaine)

Lidocaine is one of the commonly used topical anesthetics used in pain management in patients with oral mucositis. Paraquat induced oral mucositis is characterized by pain. The presence of persistent pain not only affects the patients psychologically but also decreases their incentive and the ability for oral intake. Therefore, pain control eventually encourages oral intake, thus improving nutrition and reducing further complications. The different formulations of lidocaine (sprays, solutions, gels and ointments) provide clinicians with options to choose for the most effective formulation for maximal effect; Solutions are effective when anesthetics are needed to cover a wide surface area without the risk of aspiration. Four studies showed the benefit of lidocaine in reduction of pain and severity of oral mucositis.^{19 20 21 24} The first two studies compared lidocaine gargle as compared to bland rinses and symptomatic management, the incidence of oral mucositis and pain decreased in both trials by 23.33% and 40% respectively.^{19 20} The other two studies in-cooperated lidocaine as one of the ingredients for a compounded preparation, both studies reported adequate pain management.^{21 24} The main adverse effects associated with lidocaine are burning and stinging on the local site of administration, loss of taste due to anesthetization of the taste buds, and suppression of gag-reflex if the posterior oropharyngeal area is anesthetized.²⁶

Dexamethasone

Dexamethasone, a corticosteroid, acts by bringing about the glucocorticoid effects. Glucocorticoids have potent anti-inflammatory actions, including the reduction in the number and function of various immune cells, such as T and B lymphocytes, monocytes, neutrophils, and eosinophils, at sites of inflammation. Glucocorticoids decrease the production of cytokines, chemokines, and eicosanoids and enhance the production of macrophage migration inhibitory factor.²⁷ Due to its therapeutic anti-inflammatory properties dexamethasone may aid in decreasing the severity of paraquat induced oral mucositis. We identified three main studies. The first trial evaluated the effects of early administration of dexamethasone (experimental) as compared to delayed administration (control). It was noted that the experimental group, that received dexamethasone mouth rinse at presentation and consecutively for three days showed a significant decrease in mucosal lesions and therefore a reduction of associated pain.²³ The other two studies combined dexamethasone with other ingredients in order to form a compounded preparation that substantially reduced the incidence and severity of oral mucositis.^{16 21}

Chinese herbal remedies

Kangfuxin

Kang fu xin is a pure Chinese herbal medicine extracted from *Periplaneta Americana* (the American cockroach) and is used in the treatment of several ulcerative conditions. The key components of Kangfuxin are polyhydric alcohols, peptides, mucin, amino acids and other active substances. Kangfuxin improves the gastrointestinal mucosa microcirculation, promotes the growth of granulation tissue and angiogenesis, it accelerates shedding of necrotic tissue, therefore expediting the wound or ulcer healing process. This accelerated wound healing process and gastro- protective properties play an important part in the treatment of oral, gastric and duodenal ulcers.²⁸Kangfuxin has also been noted to significantly increase the production of superoxide dismutase which has anti-oxidant and anti-inflammatory properties. ²⁸In addition, its anti-inflammatory properties not only reduce associated inflammatory edema but also aid in pain reduction. Kangfuxin solution can also be used in the formation of compounded mouth washes, this formulation aids in the management of oral erosions and ulcers caused by paraquat ingestion. ²⁹We recognized two clinical trials that used Kangfuxin in the management of paraquat induced oral mucositis. Both studies used Kangfuxin for oral care prior to the application of the other intervention. ^{18 28} All two trials reported positive outcomes in terms of reduction in oral mucositis severity and improvement of healing time.

Tea oil (Camellia oil)

Tea oil also known as camellia oil or camellia seed oil is natural herbal oil extracted from *Camellia oleifera* Abel. It has been used through history mainly because of its anti-inflammatory and anti-oxidant properties. Squalene, polyphenols and flavonoids present in camellia oil have good bactericidal and anti-inflammatory effects, these effects ward off secondary infections and also aid in the reduction of associated pain. ^{30 31} ³²The protective properties of camellia oil in relation to its antioxidant activity help neutralize the excessive production of Reactive Oxygen Species and ulcerative destruction of the already compromised mucosa after the ingestion of paraquat. One clinical trial was recognized. The clinical trial used tea oil as one of the ingredients in a compounded paste preparation. 20 mls of tea oil was used in the preparation and the paste was used 3-5 times a day. The control group only received oral care using qingkou gargle. The results of this randomized study showed significant difference for average number of days to mucositis resolution or pain scores. ²⁵

MEBO (moist exposed burn ointment)

MEBO is an herbal formulation containing b-sitosterol, baicalin, and berberine as active ingredients in a base of beeswax and sesame oil.³³ MEBO not only has analgesic and antimicrobial effects but also has been noted to promote the formation of granulation tissue and therefore shorten the healing duration of ulcers and wounds. It increases gene expression of vascular endothelial growth factor and basic fibroblast growth factor (bFGF), which help in the regulation of angiogenesis and tissue repair. ^{2834 35} It can be directly applied on the surfaces of the oral ulcers induced by paraquat or prepared into a compounded formulation. One clinical trial used kangfuxin and MEBO for the management of oral mucositis. The treatment group used Kangfuxin for oral care prior to the application of MEBO that was used to adequately cover the oral mucosa 3 times/day. The control group only used Kangfuxin for oral care. MEBO proved to be effective alternative in the treatment of paraquat induced oral mucositis.²⁸

Colloidal silver (yin er tong/ activated ionized silver)

Silver and is a non-antibiotic antibacterial agent that has been used through history for its antimicrobial effects. ³⁶Through time, its use diminished after the discovery of penicillin and other antibiotics. With the rising cases of antibiotic resistance, the use of silver and other non-antibiotic antibacterial treatments have been on the rise as an alternative for antimicrobial coverage.³⁷Colloidal silver, silver nanoparticles and ionized silver, exhibit a broad-spectrum antimicrobial capability against many micro-organisms (gram-positive bacteria, gram-negative bacteria, fungi and rhinovirus). ^{38 39} The effectiveness of silver's broad-spectrum antimicrobial capability is attributed to ability of the silver ions in binding non-specifically to

many different targets, thus affecting bacteria in many components of their metabolism and structure.⁹⁴ One clinical trial used yin er tong in conjunction with other interventions in the management of oral mucositis. The treatment group received yin er tong, recombinant human epidermal growth factor, Kangfuxin and Vit C, while the control group received conservative management for their symptoms. The patients were asked to gargle with 10 mls of yin er tong for 3-5 minutes for approximately 3 times a day. The treatment group was more effective in terms of pain reduction and severity of oral mucositis.¹⁸

Antimicrobial prophylaxis

The administration of antibiotics for prophylaxis is a common practice in the management of oral mucositis. The premise for the use of antibiotics is mainly to mitigate or prevent infection or microbial colonization. Microbial colonization is likely to intensify the inflammatory process as well as exacerbating and perhaps even causing extensive ulceration to the already injured mucosa. To date, evidence is still conflicting concerning the use of prophylactic antibiotics. Most centers still administer antibiotics to all patients who present with mucosal injury despite the lack of evidence.⁴⁰⁷⁵ We recognized two studies that used gentamicin and metronidazole for antibiotic prophylaxis. Both treatment group in the clinical trials used gentamicin in a compounded multi-agent mouth wash. The outcomes for the two trials reported positive results in terms of pain management, infection control and reduced severity of oral mucositis.^{16 21} One clinical trial highlighted the need for mucosal cultures for targeted antimicrobial treatment for patients who present with oral ulcerations after paraquat ingestion.

Montmorillonite and smecta

Montmorillonite and smecta is a natural clay mineral belonging to the smectite group. Smectites are natural clay minerals that have several clinical applications in medicine (absorbents, antacids and antidiarrheal). The compounds are absorbents (enterosorbents), their high absorption capacity aid in the absorption of toxins within the gastrointestinal tract. The contact effect of medical clay on the GI mucosa creates a protective layer on the mucosa, therefore also serving a protective purpose. Due to their muco-adhesive nature, smectites create a barrier and prevents further damage on the mucosa. Smectite compounds also have antibacterial and antiviral properties in that they bind to the pathogens and allow enhanced elimination of the microbes and therefore reducing the chances of possible secondary infections. Smectites have not only been found to be useful in gastrointestinal mucosa, but compounded mouthwashes containing these compounds also play an important protective role to the oral mucosa.⁴¹⁴² The first clinical trial used montmorillonite as a base for a compounded paste. 5 grams of montmorillonite was used in conjunction with tea oil and Vit C for the formulation. In the treatment group the paste was used to adequately cover the oral mucosa and ulcer surfaces three times a day for duration of five days. The paste gave a positive outcome in terms of pain reduction and improved healing time for the patients.²⁵ The second trial used smecta powder 2-3 times a day to adequately cover the oral mucosa in conjunction with other interventions. The trial also had positive results in the management of oral mucositis.

Epidermal growth factors

Epidermal growth factors play a fundamental role in wound healing through stimulating epidermal and dermal regeneration, which participates in dermal wound healing and dermal regeneration through stimulation, proliferation, and migration of keratinocyte, endothelial cells, and fibroblast.⁴³ Several clinical trials have shown that epidermal growth factor is an important cytoprotective factor against injuries, and contributes to wound healing and maintenance of mucosal integrity in the oral cavity and the gastrointestinal tract.⁸² Topical application of epidermal growth factor on the oral mucosa in combination with other conventional treatments may promote mucosal healing, reduce the severity of intraoral manifestations, and is therefore an effective treatment option in paraquat induced mucositis and ulcerations.⁴⁴ We recognized two studies that used recombinant human epidermal growth factor spray in the management of paraquat induced oral mucositis. The first study used recombinant human epidermal growth factor spray 3 times a day in conjunction with other intervention. It was noted that the incidence of oral mucositis decreased by 12.8%.¹⁸ The second trial used recombinant human epidermal growth factor spray two times a day for patients who

presented with no oral mucosal erosions or ulcerations and three times a day for patients who presented with ulcerations. It was evident that recombinant human epidermal growth factor improved healing time and therefore reduced the severity of symptoms of oral mucositis.

Topical Vitamin C

Vitamin C (ascorbic acid) is an important water soluble micronutrient that plays several roles in the human body. It is an antioxidant and a free radical scavenger and serves as an essential cofactor for many enzymatic reactions through iron-, copper- and 2-oxoglutarate-dependent dioxygenases. Mucosal damage after paraquat ingestion is not only due to its caustic nature but also paraquat ingestion causes an accumulation of free radicals which exacerbate inflammation causing extensive mucosal and tissue damage. Vitamin C neutralizes those free radicals generated after paraquat ingestion therefore enhancing body's antioxidant stores in order to prevent mucosal damage and to maintain healthy oral tissues.^{25 45} Vitamin C also plays an important role in immunomodulation, and its deficiency results in impaired immune responses.⁴⁶ Ascorbic acid plays an important part in wound healing; this is mainly attributed to its role in collagen synthesis and the hydroxylation of lysine and proline.^{47 48} These three major roles; antioxidant, immunomodulation and wound healing, are significant in the treatment of mucosal damage induced by paraquat. Two clinical trials were highlighted. The first trial used 0.2 Vit C that was taken orally three times a day.¹⁸ The second trial incorporated 5 grams Vit C as one of the ingredients in the formulation of a compounded paste.²⁵ Both trials reported positive outcomes in relation to pain reduction and oral mucositis severity.

Discussion

The primary objective of treatment for mucosal injury after the ingestion of paraquat focuses on pain management, decreasing inflammation, antibiotic prophylaxis, antioxidant therapy and removal of accumulated necrotic tissue.^{17 1949} Currently, there is no consensus on a treatment protocol for corrosive oral mucosal after the ingestion of paraquat. Different protocols exist, but the basis of all the different protocols carries the same backbone which aims at maximum pain control for the patient, prevention of further damage, and prevention of complications that may arise.⁵⁰

Despite oral care and medical intervention being important treatment modalities for oral mucositis, other factors like nutritional and psychological support also play an important role. Feeding difficulties due to dysphasia and odynophagia is one of the major complications that come about from the ingestion of paraquat.⁵¹ Patients who are able to feed normally should avoid any irritants like spicy foods, acidic or tart food, dry or rough food, tobacco, alcohol and alcohol based mouthwash. Patients should also be encouraged to have adequate fluid intake, which will be essential in maintaining the patients hydration status and also ensure that the oral mucosa is adequately hydrated. Patients should be initially be started on smaller, frequent, energy and protein dense meals or snacks in order to attain their caloric needs.⁵² The consistency and temperature of food should also be altered to be in tune with the patients tolerances (for example cool or lukewarm temperature, soft solids, mashed solids, pureed solids foods).¹⁷ For those with extensive oral mucosal injury and are unable to feed normally, nutrition can be achieved by either enteral or parenteral nutrition. Enteral nutrition involves the delivery of liquid formula beyond the esophagus, in an area where the gut is functioning normally and is without injury. This is achieved through the use of either a feeding tube or a stoma. Parenteral nutrition (TPN) refers to the delivery of calories and nutrients intravenously through peripheral or central veins.^{16 1718 19}

Paraquat poisoning is usually seen in suicidal attempts, where the patients intentionally expose themselves to the compound. These patients' psychiatric state is fragile and unstable. After admission, caregivers should ensure that the patients are in a safe environment. Safety can be ensured by the removal of anything that can be fashioned into a weapon, and also any medication that could be used for deliberate self-harm. All patients should be monitored frequently. Treatment of underlying psychiatric or psychological issues should be initiated as early as possible. The provision of good psychological support has been shown to be beneficial

for patients by reducing both psychological distress and physical symptoms through increasing quality of life and enhancing coping mechanisms in relation to stress and pain.^{53 54}

The primary findings through our systematic review clearly indicated that most of the studies used a multi-drug combination for the interventions. These studies incorporated the use analgesics mainly lidocaine, Chinese traditional herbal remedies, growth factors, corticosteroids and antioxidants. Seven studies in total used compounded formulations in their management with the two main components of the compounded formulation being a bland rinse like normal saline and lidocaine.^{16 19 2125 24 2355} The main advantage with compounded formulations is that they integrate the use of different drugs and also they formulations are able to cover a wider surface of within the oral cavity. Because of the integration of the different drugs, compounded formulations not only actually did improve the healing time as well as pain control as compared to the control and the placebo groups. Despite the popularity of compounded formulations other studies still showed promising results with the use of individual multi-drug management. Chinese herbal remedies and other natural remedies play an important role too in the management of paraquat induced oral mucositis. Many studies have assessed the use of herbal and natural remedies in the management of oral mucositis. Our highlighted studies have shown that herbal and natural remedies, like kangfuxin, MEBO, ying er tong and tea oil and their associated anti-inflammatory, anti-oxidant and antimicrobial properties make them ideal interventions that can be used in conditions that cause oral mucosal ulcerations.^{18 16 25 28}

Although there is no consensus on the management of paraquat induced oral mucositis, we believe that this systematic review will provide guidance on the possible effective interventions, and also be a stepping stone to further studies in order to determine the roles of possible new therapies.

Possible future interventions

Superoxide dismutase

Superoxide dismutase is one of the first line defense antioxidants alongside catalase and glutathione peroxidase within the cells, which is basically an enzyme that catalyzes the dismutation of superoxide radicals which are reactive oxygen species into oxygen, hydrogen peroxides and hydroperoxides. Catalases then ensure the breakdown of hydrogen peroxides into water and oxygen. Clinically, superoxide dismutase may provide essential antioxidant effects especially in conditions that cause an increased accumulation of reactive oxygen species thus creating oxidative stress within the cells.⁵⁶ A study by Hong Mei et al confirmed that the antioxidant effect of superoxide dismutase is essential in the mitigation of paraquat induced inflammation in the oral mucosa of animals.⁵⁷ This shows that superoxide dismutase has the potential of playing an important therapeutic role in paraquat mucosal damage, and further studies and investigations are warranted.

Limitations

At presentation, patient stabilization, history taking concerning timing, the quantity of paraquat ingested and detailed examination of presenting signs and symptoms (the presenting condition of the lips, tongue mouth, and oropharynx) is prudent. The absence of erythema, ulcerations, or lesions should not completely exclude the possibility of mucosal injury, and close oral assessment and observation should be done promptly and routinely. This is mainly because the appearance of pathology is not always consistent and is dependent on the dosage and the concentration of the paraquat ingested. As previously mentioned, the appearance of lesions and ulcers may occur from hours to 2-5 days after ingestion.

Conclusions

Paraquat is a caustic agent that produces corrosive injuries to the oral mucosa and the upper gastrointestinal mucosa. The associated injury to the mucosa is painful, and with that affects patients' nutrition and quality of life. To date, there is no definitive protocol for the treatment of mucosal injuries due to paraquat ingestion,

with different hospitals and centers having different protocols. Our systematic review analyzed and hoped to highlight the different interventions that can be used in the management of paraquat induced oral mucositis. Our main findings were that the main method of management was the implementation of a multi-drug regimen, which was mainly through the use of compounded preparations or a polydrug system. The review also highlighted the importance of herbal and natural remedies, and that their proper use can be beneficial in a clinical setting. The studies found were relatively small RCT's, further detailed research towards paraquat induced oral mucositis should be undertaken, with the hope of finding a consensus on the appropriate interventions and management.

Clinical trial registration

Not applicable.

Permission to reproduce material from other sources

Not applicable.

Patient consent statement

Not applicable.

Ethics approval statement

Not applicable.

Data availability statement

Data availability is not applicable to this article as no new data were created or analyzed in this study.

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Not applicable.

Conflict of interest

None.

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Table 1: Summarized studies highlighting the management of PARAQUAT induced ORAL MUCOSITIS

	Author	Study Type, Total sample size	Intervention	Route of administration	Indication / Treatment or prevention	Agents
1	Liang Yan et al 2011	Quasi-RCT N =62	Early oral care	Topical	Prevention and treatment	Multi- agent management using normal saline, yingertong, gentamicin, metronidazole and dexamethasone Appropriate dietary and nutritional measures
2	Hu ping et al 2011	RCT N = 76 patients (32 control group, 44 treatment group)	Oral care (multi-drug)	Topical and PO	Treatment	Multi-agent management using normal saline or 5% sodium bicarbonate gargle, Ultrasonic atomization of 3-5mls of distilled water, smecta powder and lidocaine. Appropriate dietary and nutritional measures Psychological support

	Author	Study Type, Total sample size	Intervention	Route of administration	Indication / Treatment or prevention	Agents
3	HE Yuan et al 2019	RCT N = 52 patients (26 control group, 26 treatment group)	Oral care (multi-drug)	Topical and PO	Treatment	Multi- agent management using 2% sodium bicarbonate solution gargle, yinertong, recombinant human epidermal growth factor spray, Kangfuxin and Vit C Appropriate dietary and nutritional measures Psychological support
4	Zhang et al 2014	RCT N = 84 patients (42 control group, 42 treatment group)	Lidocaine	Topical	Treatment	Lidocaine gargle solution Appropriate dietary and nutritional measures
5	Zhang Xiao Qing et al (2016)	RCT N=60 (30 control group, 30 treatment group)	Lidocaine	Topical	Treatment	Lidocaine gargle solution Appropriate dietary and nutritional measures
6	Li Liang et al (2015)	RCT N=45 (25 treatment group, 20 control)	MEBO	Topical	Treatment	Multi-agent management using kangfuxing and MEBO

	Author	Study Type, Total sample size	Intervention	Route of administration	Indication / Treatment or prevention	Agents
7	Huang Jian et al (2009)	RCT N=105 (55 treatment group, 50=control group)	Recombinant human epidermal growth factor	Topical	Treatment and preventive	Multi-agent management using recombinant human epidermal growth factor and lidocaine gargle solution
8	Chen Shao et al (2013)	RCT N=61 (31 treatment group, 30 control group)	Compounded preparation (dexamethasone, gentamicin and lidocaine)	Topical	Treatment and preventative	Compounded mouth wash containing normal saline, 2% lidocaine, dexamethasone and gentamicin
9	Qiu Hong et al (2018)	RCT N=40 (20 treatment group, 20 control group)	Compounded preparation	Topical	Treatment and preventative	Multi-agent management using qingkou mouth rinse and a compounded paste (tea oil, montmorillonite powder and vitamin C)
10	Liu Qing et al (2012)	RCT N=59 (30 treatment group, 29 control group)	Dexamethasone	Topical	Treatment and preventative	Dexamethasone gargling solution

Table 2: Population, Intervention, Comparison, Outcome (PICO) model to evaluate the effectiveness of different treatment modalities in the management of PARAQUAT induced ORAL MUCOSITIS

	Author (Year)	Population	Intervention	Comparison	Outcome
1	Liang Yan et al 2011 ¹⁶	Quasi-RCT N =62	To compare the efficacy of early oral care as compared to delayed oral care in PARAQUAT induced ORAL MUCOSITIS Intervention< 3 days post ingestion patients has no signs of oral mucositis Normal saline and ying er tong gargle alternatively three times a day Gentamicin 80000 u, metronidazole 4g and dexamethasone 5mg aerosol inhalation, twice a day	Interventions >3 days after ingestions. Patients have signs or erosion and oral mucositis Mixed drug compounded gargle twice daily: (Metronidazole 4g and gentamicin in normal saline 2) Lidocaine 100 mg in 200-500ml normal saline. Vitamin B1 10-20 mg 3times/day	Significant reduction in formation and severity of oral mucosal lesion in the experimental group
2	Hu ping et al 2011 ¹⁷	RCT N = 76 patients (32 control group, 44 treatment group)	To evaluate the efficacy of proper oral care. Normal saline or 5% sodium bicarbonate gargle 3 ~ 4 times / day Ultrasonic atomization of 3-5mls of distilled water for 10 minutes 2-3 times/day Coating using smecta powder 2-3 times a day Lidocaine for pain relief prior to meals	symptomatic management	Treatment group was more effective in the reduction of pain and other symptoms. Treatment group 79.5% Control group 28.1%

	Author (Year)	Population	Intervention	Comparison	Outcome
3	HE Yuan et al 2019 ¹⁸	RCT N = 52 patients (26 control group, 26 treatment group)	To evaluate the efficacy of proper oral care. 2% sodium bicarbonate solution gargle Gargle with 10 mls yinertong for 3-5 minutes recombinant human epidermal growth factor spray 3 times/day Kangfuxin for tooth brushing Vit C 0.2g PO 3 times/day	Symptomatic management	Treatment group was more effective in the reduction of pain and other symptoms. Treatment group (92.17±3.25) Control group (79.37±2.38)
4	Zhang et al 2014 ¹⁹	RCT N = 84 patients (42 control group, 42 treatment group)	To evaluate the efficacy of oral care using lidocaine. Lidocaine gargle solution 100ml normal saline solution added 5 mls of 0.1g lidocaine gargles for 3 mins every 2 hourly	Patients gargled with 5% sodium bicarbonate twice daily	Treatment group was more effective in pain reduction and healing time. Treatment group 88.10% Control group 66.67%
5	Zhang Xiao Qing et al (2016) ⁵⁵	RCT N=60 (30 control group, 30 treatment group)	To evaluate the efficacy of oral care using lidocaine. Lidocaine gargle solution : 2% lidocaine in 100 mls of NS gargled for 3 mins every hourly	Symptomatic management	Treatment group was more effective in pain reduction and healing time. Treatment group 93.33% Control group 53.33%

	Author (Year)	Population	Intervention	Comparison	Outcome
6	Li Liang et al (2015) ²⁸	RCT N=45 (25 treatment group, 20 control)	To evaluate the effectiveness of kangfuxin and MEBO in PARAQUAT induced ORAL MUCOSITIS Patients initially gargled with kangfuxin and the oral mucosa was adequately covered with MEBO 3 times/day for a week	Patients only gargled using kangfuxin	MEBO and kangfuxin proved to be effective in the prevention of oral ulcers and therefor improving healing time
7	Huang Jian et al (2009) ²⁴	RCT N=105 (55 treatment group, 50=control group)	To evaluate the effectiveness of recombinant human epidermal growth factor and lidocaine in PARAQUAT induced ORAL MUCOSITIS Recombinant human epidermal growth factor sprayed twice daily for patients without oral ulcerations and 3 times/daily for patients with oral ulcers 10 mls lidocaine in 100 mls of normal saline gargled 2 times/day for 3 minutes	Patients gargled with 5% sodium bicarbonate twice daily	Recombinant human epidermal growth factor and lidocaine proved to be effective in pain reduction and improving healing time.

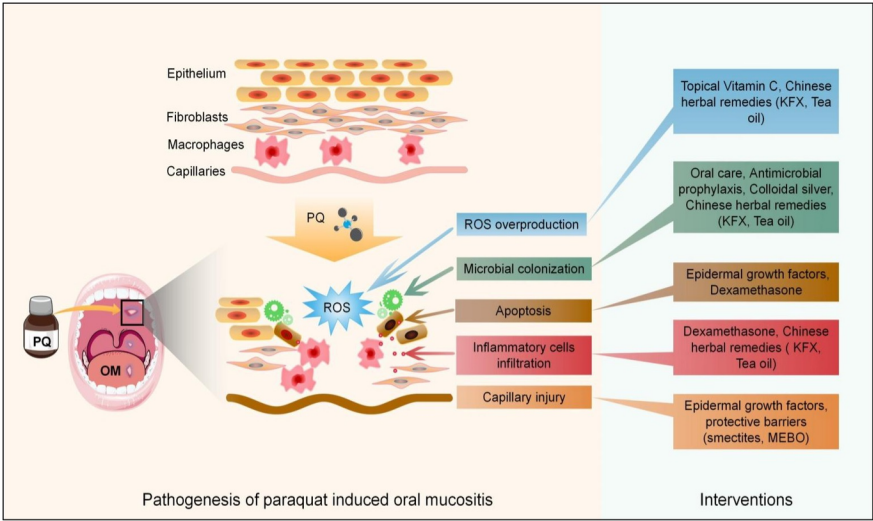
	Author (Year)	Population	Intervention	Comparison	Outcome
8	Chen Shao et al (2013) ²¹	RCT N=61 (31 treatment group, 30 control group)	To evaluate the effectiveness of lidocaine, dexamethasone and gentamicin in PARAQUAT induced ORAL MUCOSITIS Mouthwash (250 mls of 0.9% normal saline, 5 mls of 2% lidocaine, 5mg dexamethasone and gentamicin) to be gargled every 4 hourly for a duration of 5 minutes	Mouthwash (250 mls of 0.9% normal saline and 5mg dexamethasone) to be gargled every 4 hourly for a duration of 5 minutes	Treatment group was more effective in pain reduction and healing time as compared to the control group
9	Qiu Hong et al (2018) ²⁵	RCT N=40 (20 treatment group, 20 control group)	Therapeutic effects of tea oil, montmorillonite and Vit C. Patients asked to gargle with 15 mls of qingkou mouth rinse 3-5 times/day The oral mucosa and the ulcers surface were covered by a compounded paste (10 ~ 20 ml tea oil and 5g of montmorillonite powder and 5 g vitamin C)	Patients asked to gargle with 15 mls of qingkou mouth rinse 3-5 times/day	Treatment group was more effective in pain reduction and healing time as compared to the control group

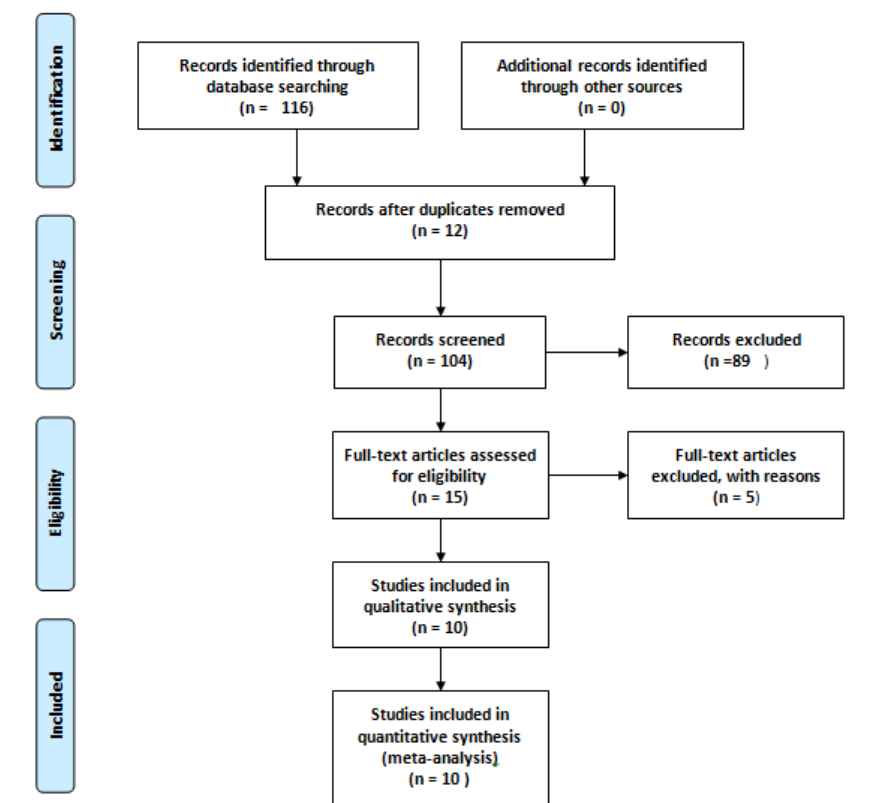
	Author (Year)	Population	Intervention	Comparison	Outcome
10	Liu Qing et al (2012) ⁵⁸	RCT N=59 (30 treatment group, 29 control group)	Effectiveness of gargling dexamethasone solution in relation to the reduction of mucosal injury. Patients asked to gargle with dexamethasone 10mg in 250ml normal saline every 4 hours for 5 minutes.	Patients asked to use normal oral care methods like the use of normal saline gargle	Treatment group was more effective in pain reduction and healing time as compared to the control group

Figure 1: Pathogenesis of PARAQUAT induced ORAL MUCOSITIS and the related inter-ventions

Figure 2: Preferred reporting items for systematic review (PRISMA) diagram showing article selection for PARAQUAT induced ORAL MUCOSITIS

Figure 3: Risk of Bias assessment across individual studies





	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Hong Qiu 2018	?	?	?	+	+	+	+
Jian Huang 2009	?	?	?	+	+	+	+
Jinzheng Zhang 2014	?	+	?	+	+	+	?
Lianxiang Li 2015	?	?	?	+	+	+	+
liuqing Huang 2012	?	?	?	+	+	+	+
Ping Hu 2011	?	?	?	?	+	+	+
Shaojuan Chen 2013	?	?	?	+	+	+	+
Xiaoqing Zhang 2016	?	+	?		+	+	+
Yan Liang 2011	-	?	?	?	+	?	+
Yuan He 2019	?	?	?	?	+	+	+