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Low exposure levels of respirable particles during the preparation of NexoBrid® bromelain powder

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Abstract

Background: Burns are common injuries that are usually covered with a layer of necrotic tissue called the eschar. Early removal of the eschar is the current standard of care, however, debridement using tangential excision is usually traumatic and may increase wound surface. In recent years a bromelain-based debriding agent called NexoBrid® that can remove the eschar selectively and thus causes less additional trauma was developed. Bromelain is a pineapple-stem derived mix of proteases. In its raw form bromelain is a yellowish powder. Cases are known where frequent inhalation of bromelain dust led to respiratory sensitization and subsequently to severe allergic reactions. In order to activate bromelain for debridement it has to be mixed with a hydrating gel. We aimed to assess the risk of sensitization by measuring the particle concentration in the air during the mixing process in order to determine the safety of the product for patients as well as practitioners.

Methods: The mixing process was repeated five times in a row. Samples of the particle concentration in the workers breathing area were taken with an air particle counting device during continuous performance. The worker wore a lab coat and gloves but no face mask.

Results: Particle concentrations ranged from 0.010 mg/m^3 to 0.012 mg/m^3 (mean 0.010 mg/m^3). The particles were chemically termed as "respirable dust".

Conclusions: We measured very low exposure levels of inhalable particles during the mixing process. Because the particle counter could not distinguish the components of the dust, it is possible that also background particles contributed to the results. A review of literature revealed that relatively high exposure levels are necessary for respiratory sensitization, whereas also low exposure levels may exacerbate an allergic reaction. We suggest that preparation of NexoBrid® is safe as long as standard safety precautions are met. Patients with known allergy to pineapple should be treated more carefully to prevent an allergic reaction.

Keywords: Burn, Burns, Bromelain, Allergy, Asthma

Background

Bromelain as debriding agent in burns

Thermal traumas are common injuries. In the United States alone there were half a million burns recorded in 2014; of which 200,000 patients were admitted to burn centers [1]. Improvements in care, including early excision and autografting, caused a significant decrease of morbidity and mortality rates [2]. Nevertheless, excessive scarring leading to functional restrictions and disfigurement are issues that need to be solved in burn care currently [3].

In contrast to mechanical wounds, second and third degree burn wounds present clinically with a layer of necrotic tissue called eschar. This eschar makes accurate diagnosis of burn depth challenging, which may put the patient at risk for local and systemic complications [3, 4]. Furthermore, non-excised eschar contributes to burn wound progression, which is associated with a conversion from deep-partial thickness burns into full-thickness

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burns [4]. Modern burn care standards recommend early debridement followed by autografting as standard of care. For deep partial thickness burns, eschar removal is done in the operation room, usually by tangential excision, until bleeding or viable tissue is reached. However, this surgical technique has its drawbacks: excisional debridement is traumatic and associated with vast amounts of blood loss, especially if hemostasis is not performed properly. In addition, surgical wound debridement requires trained surgical personnel and adequate tools [3]. Viable tissue is prone to damage during tangential excision. Studies showed that about half of the surgically excised burn wound tissue was viable [4]. In some cases, surgical debridement has to be delayed until accurate diagnosis of burn depth can be performed in order to determine whether there is a need for fascial excision.

Chemical and enzymatic approaches have been tried to speed up this process. Initial approaches toward enzymatic debridement used a combination of papain, sodium salicylate and cysteine hydrochloride. Earlier enzymatic debriding agents were slow, and thereby useless for early burn wound debridement [4], and even increased the risk of infections via maceration of the eschar [3].

In recent years, the bromelain-based debriding agent NexoBrid® has revolutionized enzymatic burn wound debridement. It allows fast and early debridement of second to third degree burn wounds. Recent studies demonstrated that NexoBrid® removed the burn eschar significantly faster than other enzymatic techniques. Compared to surgical debridement, it decreased the need for further surgical excision as well as the amount of excised tissue significantly. Further, the authors showed that in patients treated with NexoBrid® surgery related blood loss was significantly lower in comparison to the standard of care treated patients [3]. In an animal study on pigs, the use of the enzymatic debriding agent lead to a preservation of the zone of stasis and subsequent lack of burn wound progression [4]. In a similar trial, the bromelain agent NexoBrid® also lead to significantly faster reepithelialisation of partial thickness burns as compared to a bromelain-free vehicle gel [5].

What is bromelain?

Bromelain is the aqueous crude extract from the stems of immature pineapple plants. It consists of glycoproteins and carbohydrates, as well as a complex mixture of enzymes including phosphatases, glycosidases, peroxidases, and cellulases [6]. Since its introduction, bromelain has been widely used in pharmaceutical industries, food production and in diagnostic laboratories [7]. Nowadays bromelain is extracted from cooled pineapple juice rather than pineapple stems. After a process involving centrifugation, ultrafiltration, and lyophilisation, bromelain is maintained as a yellowish powder. The activity of the bromelain enzyme can be determined with different agents such as casein (FIP units), gelatine (gelatine digestion units), or chromogenic tripeptides [6, 8].

For medical purposes, various therapeutic effects of bromelain are used: It has shown beneficial effects on circulation and blood coagulation such as prevention and reduction of edema as well as being a supporter of fibrinolysis and inhibitor of platelet aggregation. It has anti-inflammatory effects via reduction of prostaglandin E2 and thromboxane A2. In a mouse cancer model it even prevented metastases [6]. Furthermore, in children with acute sinusitis bromelain led to a faster symptom relief in comparison to the standard therapy (antiphlogistics, antibiotics and physical therapy) [9]. And decades ago pineapple juice has been used as anthelmintic agent [7]. As recent studies showed, bromelain as debriding agent in burns is becoming more and more popular [3–6, 8].

Allergy to bromelain

Studies suggest that sensitization to proteolytic enzymes takes place in the humans' respiratory tract. In literature few cases of allergic reactions caused by bromelain are described. In all cases described, sensitization to bromelain occurred due to occupational exposure to inhalable dust. The reported working environments where these incidents occurred were located in pharmacologic and diagnostic laboratories. All described cases had victims that had frequently been exposed to bromelain-containing dust [7, 10, 11]. However, not all to bromelain exposed workers developed allergic symptoms [7].

The observed symptoms following bromelain exposure ranged from rhinitis and ocular itching to severe asthmatic episodes requiring immediate medical treatment [7, 10, 11]. In some subjects, however, pineapple ingestion could trigger gastric distensions and nausea [11]. In the cases where blood testing was performed, all patients with bromelain allergy showed bromelain-specific IgE-antibodies. In most of the concerned patients, total IgE-levels were normal indicating an absence of atopic disease [7]. In diagnostic testing, symptoms occurred after exposure to inhalable particles [10], after prick-testing [7] and even after eating a pineapple [11].

Aim of study

Because the medical literature indicates that an allergic reaction to bromelain is mainly work related, we aimed to estimate the risk for personnel working with the bromelain-based debriding agent NexoBrid®. NexoBrid® has to be prepared as follows: Before application to the wound, bromelain powder needs to be mixed with an activating hydrating gel [4]. This has to be done directly before administration because bromelain deteriorates in a liquid state through self-digestion [6]. The risk of respiratory sensitization is probably related to the allergen

concentration [12]. We aimed to assess the concentration of inhalable particles in the air during preparation of NexoBrid®, to investigate whether there is a potential risk of inhalation of high concentrations of bromelain dust.

Methods

In January 2015, one worker performed routine procedures including the mixing of 5 g bromelain powder with 50 g of the gel vehicle in the original product container. The work was conducted on a normal lab bench with no local exhaust. Measurements of inhalable particles in the workers breathing zone were taken using the air particle counting device TSI Side Pack AM510 (TSI Incorporated, USA; calibrated on September 2014) (Fig. 1). The mixing process was repeated five times in a row. Each mixing cycle took 3–4 min, and sampling was done during continuous performance. The worker wore gloves and a lab coat but no face mask.

Results

The particle concentration ranged from 0.010 to 0.012 mg/m^3 (mean 0.010 mg/m^3). The particles were chemically termed as "respirable dust". Table 1 lists the test results.

Discussion

NexoBrid® provides the practitioner with the possibility of single-stage complete debridement of the burn wound. According to first results of research, the advantages of enzymatic debridement are: earlier complete debridement, less treatment-related blood loss and less need for autografting [3]. However, blood loss was only measured by the difference of hemoglobin and hematocrit before and 24 h after therapy (surgical or enzymatic debridement). The effect of administered fluid before treatment was not taken into account. Also the possibility of fluid loss due to extravasation into the tissue was ignored. Still, NexoBrid® remains the most promising enzymatic debriding agent available to date.

Fig. 1 TSI AM510 Aerosol Monitor

Table 1 Test results

Test	Concentration (mg/m^3)	Chemical Properties	Preparation Time (min)
1	0.010	Respirable Dust	4
2	0.011	Respirable Dust	4
3	0.010	Respirable Dust	3
4	0.012	Respirable Dust	3
5	0.010	Respirable Dust	3

The results obtained in our measurements during mixing of bromelain with hydrating gel indicated low exposure levels of inhalable particles. With the particle counter used it was not possible to distinguish the components of the dust. Thus it is possible that background particles contributed to the results of the measurements.

In the cases of bromelain sensitization due to exposure at work, Galleguillos and Rodriguez mentioned that none of the patients described wore any safety protection and that dust inhalation was massive [10]. The working environment of the cases described by Gailhofer et al. was not elucidated more closely, but in the workers investigated, frequent and intensive contact with bromelain dust has been reported [7]. While all authors describe bromelain as a potent sensitizer, it seems that continuous and intensive contact with the substance is the key to sensitization. In a review of the literature Arts et al. found evidence that relatively high allergen concentrations are necessary to develop a respiratory allergy. Arts et al. further suggest that prevention of high concentrations will prevent workers from developing an allergy. In people already sensitized, however, very low exposure levels may exacerbate an allergic reaction [12].

We measured low particle levels in the breathing air of a worker preparing bromelain powder, and the steps are equivalent for the preparation of NexoBrid®. We postulate that the risk of sensitization seems to be very low for the agent handling personnel. In addition, the risk for the patient to inhale bromelain particles is low, because we know that the enzymatic burn wound debridement with NexoBrid® has to be applied during sedoanalgesia; the patient would usually be wearing an oxygen mask, which prevents the patient from direct exposure. Thus, contact of the patient's respiratory mucosa with bromelain dust and thus sensitization is highly improbable. The manufacturers of Nexobrid® however do not recommend the repeated use of the agent in the same patient due to the potential risk of sensitization via the skin.

Just as bromelain, papain is a plant-derived cysteine-proteinase [6]. Inhalation of Papain is known to cause lung injuries in mice [13, 14]. Of bromelain no such effects have been described so far. Animal studies should be

carried out to investigate the effects of bromelain inhalation on the lung tissue more thoroughly.

Conclusions

Due to our findings and the results obtained from a brief literature review, we suggest that preparation of NexoBrid® requires no extra safety precautions. Still, appropriate handling of the debriding agent, including wearing of gloves and protective clothing as well as a surgical mask, is mandatory. Additional protective gear as preparation of the powdery agent under a hood is an option, however not required. Nevertheless, patients with known allergy to pineapple or bromelain should be treated more carefully to prevent allergic reactions.

Competing interests

There may be competing interests, as Yaron Shoham is involved in the company MediWound Ltd that produces the debriding agent NexoBrid®. Testing was however performed by the independent company EcoCheck Ltd not related to MediWound Ltd. Therefore it is highly impossible that Yaron Shohams relations influenced the outcomes of the study.

Authors' contributions

CS wrote the manuscript, PW provided significant literature and reviewed the manuscript, AT contributed scientific input, YS kindly arranged the trial and provided the obtained results, CDV provided significant literature, LKB provided significant literature, DBL contributed scientific inputs for interpretation of the obtained data, LPK induced the execution of the study. All authors read and approved the final manuscript.

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