Hyperbaric Oxygen Therapy (HBO) in thermal burns

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1. Background

a. Introduction

Burn wounds to the skin represent a particular aggression on the human body. As the skin is, in surface, the largest of all organs, any alteration of its integrity has a direct functional impact on other organ systems. Therapeutic strategies in burn wound management usually imply invasive procedures of a limited aesthetic and functional nature, such as excision and skin grafting.

Mortality after a cutaneous burn wound is proportional to the depth and extension of the burn wound, associated inhalation injury and concomitant other pathologies, including age and general condition of the patient.

The duration of hospital stay after a burn injury can be crudely estimated at 1 to 1.5 days for each percentage of skin surface area burned. About 20% of this hospital stay consists of acute care. For a burn wound of 30% TBSA (Total Burned Surface Area), an estimated hospital stay of 7 weeks will be followed by a total duration of treatment of about 1 year (1).

b. Clinical presentation

Traditionally, burn wounds are classified according to three different "degrees", indicating the depth of the cellular destruction induced by the thermal energy transfer. Although this classification has the advantage of being relatively simple (and largely based on macroscopic indicators such as blisters, exudate, colour and sensitivity), it does not permit in all cases to make an accurate prediction as to the possibilities of spontaneous healing of the burn wound.

Certain "second degree" burns will necessitate, if the tissue destruction is too deep, excision and skin grafting in order to ensure healing. As the duration of the healing and cicatrisation phase is an important factor in the risk of development of hypertrophic scarring, certain burn care centres have adopted a policy of early excision of all skin that appears to be deeply burned, even if it does not classify as "third degree" (2). Others advocate waiting one or two weeks before deciding which parts can be left to heal spontaneously and which have to be excised (3).

Another classification, often used in the Anglo-Saxon literature, is based on the microscopic determination of the burn wound depth; it apparently permits a better prediction of the healing prognosis. In this classification, "superficial partial thickness" burns can heal spontaneously, whereas "deep partial thickness" and "full thickness" burns need excision and grafting. Because this classification relies on histological analysis, the reliability and representativity of a few biopsies for the entire burned surface however is being questioned (4) (5).

c. Standard management and outcome

The first goal of acute care in extensive burn wounds is life-saving, by preventing shock and circulatory collapse, and ensuring a free airway in case of head/neck burns. Preventive anti-infectious measures (cleansing of the burn wound, applying antiseptic/antibiotic ointments) are taken simultaneously. Next, an emergency fasciotomy is performed in case of circulatory burns. Intensive care management of renal, pulmonary and infectious parameters as well as adequate pain and stress-relief is important.

While superficial to moderate thickness burns may heal spontaneously (by proliferation of epithelial cells from deep dermal elements - hair follicles, sweat glands), deep partial thickness and full thickness wounds (third degree burn wounds) will not heal spontaneously. The discussion whether early excision is better than delayed excision is not equivocally closed; however, common practice is that four to five days after the burn wound, all areas that are deemed "non-recoverable" are tangentially excised and a cover (either by cadaver skin homograft or synthetic skin equivalent, or by autograft skin) is placed. In case insufficient vascularisation is suspected, a temporary cover will be preferred.

Although the treatment of severe thermal injury seems to have reached a "plateau of efficacy" over the last 20 years, some novel techniques have been advocated in recent years. Negative pressure wound therapy (NPWT) has shown promising results on burn thickness conversion, infection, and healing rates; however, recent reports show, that there is a lack of evidence proving the statistically significant benefits of NPWT in burn therapy compared to conventional therapy (6).

With increasing technical possibilities and awareness, mortality of burn wounds has shifted from the early stages to a later stage, and is now predominantly caused by infectious complications and pulmonary damage (followed by multi-organ failure or MOF) related to systemic inflammation. Advancing age, burn wound extension and the presence of inhalation injury all dramatically increase burn wound mortality.

Morbidity is still high. Areas with grafted skin are subject to hypertrophic scarring and scar retraction, the grafted skin has no thermoregulation properties (sweating, vasoconstriction/dilatation) and is generally stiff, fibrotic and aesthetically unpleasant. After the graft healing, intensive and prolonged skin care and physiotherapy are necessary to prevent skin damage and joint stiffness; compression garments to prevent scar hypertrophy need to be worn almost 24 hours per day for months to years. Psychological consequences of extensive burns and subsequent scars must not be underestimated.

2. Rationale for HBO use

a. Pathophysiology

Thermal energy transfer to cutaneous cells causes cell and tissue destruction by direct coagulation and cell lysis. In the area surrounding the burn injury, interstitial oedema occurs, causing microvascular compromise, with red blood cell sludging and capillary stasis. The maximum of this microvascular compromise has been shown to occur within 24 hours (7) (8) (9).

Tissue hypoxia and ischemia occur as a result of this stasis, which increase oedema by loss of the integrity of the capillary wall (by endothelial cell contraction). Hypovolemic shock is the cause of early death after extensive burns, and fluid resuscitation (according to various possible protocols, all calling for massive amounts of IV fluid administration) are thus the mainstay of initial emergency treatment (10).

Fluid loss, by changing the oncotic pressure gradient across the capillary vessel wall, further decreases the intracapillary fluid pressure and thus increases stasis (11). As a result, areas of burnt tissue that were initially second degree (partial thickness burn), are frequently observed to progress, within the first 24 hours after the burn, into deep second degree or third degree (full thickness) burns, needing early excision and grafting in order to heal. This happens even with optimal fluid resuscitation protocols (12).

The tissue lesion caused by thermal energy induces a massive inflammatory reaction, with stimulation, margination and activation of leucocytes. The resultant production of oxygen free radicals is further enhanced in the second stage of the burn wound evolution (reperfusion). This phenomenon is partly responsible for the generalized inflammatory reactions occurring in the bowel, lungs and heart of severely burnt patients, which may lead to multi-organ failure and (semi-delayed) death (13) (14) (15) (16).

The third cause of death in burn patients is related to systemic infection during their hospital stay. Not only is there a large possible port of entry by loss of the epithelial barrier, also the immunologic state of a severely burnt patient is depressed, making him/her much more susceptible to infections (17).

An important element in the definite treatment of deep partial thickness or full thickness burns is excision of affected skin and coverage with a temporary or permanent (autograft) epithelial layer. In order for such a skin graft to "take" the underlying wound bed must be well perfused and "healthy". In cases where the oxygenation of the (a-vascular) skin graft cannot be ensured by diffusion of underlying wound bed, either by insufficient vascularisation or by an "oxygen-stealing effect" (utilisation of molecular oxygen by infectious microorganisms), the skin graft will fail, necessitating a repeat surgical intervention. With extensive burns, this is often only possible after a delay of approximately 10-14 days, needed for the healing of the donor site. This increases the risk of infection and systemic complications.

In all of these pathophysiological mechanisms, hypoxia plays a pivotal role. In ischemic tissues, re-oxygenation should be done in a rapid and massive way, in order to decrease paradoxical tissue damage by ischemia-reperfusion phenomena.
Hyperbaric oxygen therapy is currently the only therapeutic modality to ensure this acute and repeated oxygenation.

b. Pre-clinical and animal studies

i. In vitro studies

Antibacterial effect (18) (19) (20)

- Oxygen pressures as high as 200 mmHg have been shown to effectively inhibit growth and proliferation of anaerobic and facultative aerobic bacteria.
- A synergistic effect of oxygen and antibiotics has been demonstrated for clindamycin, aminoglycosids, amoxycillin/clavulanate and quinolones; this effect is not apparent for metronidazol, an antibiotic specifically developed for anaerobic infections.
- The bactericidal activity of polynuclear leukocytes is severely impaired in case of low surrounding oxygen tensions, limiting the capacity for "oxidative burst" of those cells. In fact, it has been shown that at "normal" tissue tensions of 40-50 mmHg, polynuclear leukocytes only function at half-maximal oxidant killing capacity, and that this capacity is maximal at around 300 mmHg.

ii. In vivo studies (animal)

Oedema and fluid loss
In a canine burn model of 40% TBSA, a reduction of the plasma loss of about 35% has been observed when HBO was administered in the early phase after injury (3.0 ATA, twice daily) (21). Likewise, in a variety of animal models, reduction in oedema has been noted (22) (23) (24) (25) (26).

Decreased formation of oedema and faster resolution resulted in a markedly faster return of capillary patency ($p<0.05$) in a guinea pig model (27). A reduction in burn shock and four-fold increased survival of HBO treated animals was observed in a large 30% TBSA rat study (28). A more recent rat study showed decrease in oedema after a 30% second degree burn, most prominent from the second day on (29). Hyperbaric oxygen reduced the progression of the stasis in the first 24 hours after burn injury (30).

Preservation of dermal elements and neo-angiogenesis
Already in 1967, a rat study demonstrated preservation of microvascular integrity in a deep partial-thickness burn wound model (31). Another rat study from 1988 reported preservation of dermal elements, no conversion of partial to full-thickness wounds and preservation of ATP levels in burned tissue (32). In a rat study from 1996, a deep partial-thickness burn of 5% TBSA was created in rats which progressed, in a reproducible way, towards full-thickness after 24 hours.
Comparing two groups of animals, one who received a classic burn treatment including topical antibiotic ointments and the other who received the same treatment plus HBO (2.0 ATA, 60 minutes, twice daily) for 5 days, a preservation of deep dermal elements was observed, classifying the burn still as "second degree" at day 5 in the HBO-treated animals (33). More recently, a similar study report was published, confirming the effects of HBO on the preservation of regeneratory active follicles ($p=0.009$), on the rapidity of epithelial regeneration ($p=0.048$) and on neo-angiogenesis (p:0.009) (29).

Antibacterial effects
The antibacterial effects of HBO which have been known by its use in other pathologies have been confirmed in an animal burn wound model, even though its effect was less than that of silver sulfadiazine (34). This is not surprising, since molecular oxygen does not have a direct antibacterial effect at the pressures obtained in tissues under HBO. However, HBO restores the oxido-reduction potential in the (burned) tissues, thereby maintaining the leukocyte killing capacity of PMN and preserving the natural resistance against infection (32) (35) (20) (36).
In a 30% second degree burn wound model in rats, early HBO twice per day for 2 days prevented bacterial translocation from the gut completely (37). This study confirmed earlier reports in mice (38) and rats (39). Integrity of the barrier function of the gut is affected in severe burns, and contributes to the hypermetabolic state, the increased susceptibility to sepsis and the risk of multi-organ failure of these patients (40).

Reduction of ischemia-reperfusion effects
Several animal studies have demonstrated the reduction of inflammatory (leukocyte) infiltration in the burnt tissues as well as in distant tissues (lung and bowel) (41). Oxidative damage has been evaluated in HBO-treated animals compared to classically treated animals, showing a reduction in free radical end products, TNFa and complement activation (42).

Inhalation and pulmonary injury
Considerable attention has been given to the use of HBO in inhalation injury. There is currently a fear that it may cause worsening of pulmonary damage, particularly in those patients maintained on high levels of inspired O2.
A rat model of smoke inhalation injury showed that, independently of carbon monoxide, less inflammation occurred in HBO-treated animals (43). Another rat model of 40% TBSA burn showed no increased leucocyte infiltration around pulmonary vessels after three days of HBO treatment, compared to sham-treated animals (42).

Healing time
Re-epithelialisation time may be related to the preservation of dermal elements, and thus is expected to be faster when deepening of the burn wound during the first 24-48 hours can be prevented. This is confirmed in a number of animal studies (31) (44) (27).

iii. Clinical studies

Oedema and fluid loss

In a well-described controlled human model of a small surface (TBSA 1%) burn wound, up to 40% less oedema and exudation have been observed when HBO treatment was started early (1.5 - 2 hours) after infliction of the burn wound, and continued twice daily for three days (45). This result has been independently repeated including a sham hyperbaric treatment (8.75% oxygen at 2.4 ATA) (46).
An early report on patients with various severity of burn wounds (stratified according to TBSA and prospectively sham-controlled study) showed a significant reduction of fluid requirements (average 2.2 ml/kg/%TBSA versus 3.4ml/kg/% TBSA) – a reduction of 35%, concordant with previous animal studies (47). A retrospective human study of 21 patients, of whom 10 received HBO (2.0 ATA, 90 minutes, twice daily) in the acute phase, confirmed this reduction in needed perfusion volumes (48).
A large Chinese study comparing 266 HBO treated burn patients with 609 non-HBO treated patients over a period of 6 years, reported (no precise data given) a reduction of fluid requirements of 30% to 35% (burns with a mean TBSA of 34-36%), with improved hemodynamics and more rapid recovery of the mesenteric circulation (as judged by the return of bowel sounds and earlier nasogastric alimentation possibility) (49).
The initial experience of a major burn centre, when integrating HBO into the early treatment protocol of its patients, illustrates the importance of this "fluid-saving" effect: the first patients had a high incidence of respiratory insufficiency which turned out to be due to pulmonary fluid overload – as the classical "rules" of calculating the volume of fluid resuscitation were initially applied (50) !

Reduction of ischemia-reperfusion effects

In 8 HBO treated burn patients, of whom 4 had inhalation injury, 14 pre - and post-HBO measurements of lipoperoxidation products (both in exhaled air and in serum) found no evidence of oxidative stress (51).
Positive effects of HBO on systemic inflammatory parameters have been further confirmed with a reduction in soluble IL-2 receptor and preservation of fibronectin in burn patients. HBO treated patients had a lesser incidence of sepsis ($p<0.05$) (52).

Inhalation injury

Ray and colleagues have analysed severe burns being treated for concurrent inhalation injury, thermal injury, and adult respiratory distress syndrome, and noted no deleterious effect in those patients on continuously high-inspired oxygen. More rapid weaning from the ventilator was possible in the HBO treated group ($p<0.05$) (53).
However, HBO treatment of severely ill (ventilated) patients is not without risk, and in monoplace chambers many of these patients could not be treated (47) (48). Even in multiplace chambers, reports of severe complications in unstable patients illustrate that transfer of these patients outside the burn ward and installation/treatment in a hyperbaric chamber necessitates meticulous monitoring and pro-active care (54).

Healing rate

Indirect markers of cost are length of hospital stay and number of surgical interventions. One small prospective sham-controlled study reported significant reductions in both when using HBO (47). A large retrospective comparative study reported shorter hospital stay (47 vs 59 days) in a group of severely burnt patients (117 HBO vs 169 non-HBO, 35-75 %TBSA), however, this failed to reach statistical significance ($p>0.05$) (49). When analysing a group of simultaneously injured burn patients (10, from a military incident), the authors noted that the patients treated with HBO (about half) could be discharged at least 20 days earlier than the group not treated with HBO (for logistic reasons), even though the HBO-treated patients had larger %TBSA burned (20-30% vs 10-20%).
Two other studies, with retrospectively paired control patients, reported no difference in length of hospital stay. One of these mentioned a significantly reduced need for surface to be grafted (in a patient population with average of 30% full thickness burns) (55); the second study has been criticised for having a very aggressive excision strategy and having started HBO maybe too late (56).

Mortality rate
Results from an Australian pilot study have been reported to decrease the mortality rate in HBO-treated patients (67 patients over 2 years, 10-75 %TBSA) to 4.4%, compared to 31.3% in a retrospective control group with similarly age and %TBSA burns (113 patients over the three years previous to HBO) (p=0.002) (57). The largest retrospective study to date, from China (49), showed no significant change in mortality if all HBO-treated patients (n=266) were compared to all non-HBO treated patients (n=609); however, when analysing the severely injured patients (35-70 %TBSA, 117 HBO vs 169 non-HBO), a significant decrease in mortality rate was noted (6.8% vs 14.8%, p=0.028). Another retrospective review (abstract only, no real data available) reported a 50% reduction in mortality rate since using HBO therapy, from 14.8% to 6.8% (58). While these retrospective reports are consistent with the earliest reports (47) (48), another other retrospective controlled study did not confirm this. However, this study did confirm that while their initial experience with HBO seemed to result in higher mortality, this was refuted by their subsequent study (56).

Cost of treatment
Two studies specifically addressed the costs of burn treatment in patients with or without HBO. A first analysis, comparing all patients with burns of TBSA 18-39%, a reduction of overall average costs of 10.850 USD was observed (average hospitalisation duration 20.8 vs 33 days) (59). In the same institution, analysing a patient population matched for age, %TBSA and % full thickness burn, HBO treatment, although adding on average 8.500 USD to the hospital bill, reduced overall average cost per patient by 31.600 USD (from 91.960 to 60.350 USD - 1987 figures). This was attributed to reduced number of surgeries and shortened hospital stay (60).

iv. Other considerations

A reduced need for skin grafting may be most beneficial in burn wounds to highly functional body parts and extremities, such as hands and fingers, face and ears (61). Because of the often axial vascularisation patterns, these areas are vulnerable to oedema and ischemia by compartment syndrome. Secondary ischemia may be prevented by HBO, as in the case of compromised flaps and grafts. This would limit the need for (early) debridements and subsequent reconstruction of lost tissue.

Hyperbaric oxygen may also be used in a delayed period, for optimising wound bed granulation in preparation for skin grafting, especially when large surfaces of skin need to be grafted in sequential surgery settings, owing to the limited availability of "harvestable" skin. Optimising the wound bed prior to grafting reduces the risk of skin graft loss; HBO treatment postoperatively increases the rate of healing of the donor sites making possible earlier repeat harvesting.

3. Evidence – based review

An online Medline search (PubMed) was performed with the following key phrases and their combinations: "hyperbaric oxygen", "HBOT", "HBO", "burns", "thermal", "treatment". Types of articles retrieved were Case Reports, Clinical Trials, Comments, Comparative Study, Dataset, Editorial, Journal Article, and Review. Review articles were scanned for other possibly relevant, non-indexed references. Other databases searched were the Rubicon Research Repository, the GTUEM Database of Clinical Literature, and Hyperbaric or Diving Scientific (EUBS, UHMS) Meeting Proceedings from 1980 on.

In total 184 articles were identified from the initial literature search. Of these, 230 were discarded as not being directly relevant. Single or small number case reports were likewise not considered in this review, as they merely serve to illustrate some of the principles outlined above, without adding to the evidence base.

Based on titles and abstracts, 16 retrieved references dealing with human subjects were classified into

1. Low level of evidence:
   1.1. Case series: 3 articles (54) (58) (50)
2. Moderate-low level of evidence:
   2.1. Non controlled clinical studies (case series, retrospective non controlled studies): 2 articles (59) (49)
   2.2. Non randomized controlled studies (historical control): 3 articles (47) (48) (57)
   2.3. Randomised control studies with severe methodological problems or incomplete reporting of procedure/numbers: 2 articles (52) (62)
3. Moderate-high level of evidence:
   3.1. Non randomised controlled studies (paired/matched control): 3 articles (56) (55) (60)
   3.2. Randomised Non Controlled trial: 1 article (45)
   3.3. Prospective Randomized Controlled Blinded trial : 2 articles (46) (47)

An overview of the search strategy and results is given in Figure 1.

Articles included in the qualitative syntheses were listed in Table 1.

4. Patient selection for HBO

Based on current evidence, patients with burns of more than 20%, but of less than 50% TBSA are the best candidates for adjunctive hyperbaric oxygen therapy, as fluid loss and morbidity is high, but hemodynamics are not necessarily severely compromised. Based on the available experimental and clinical reports, most benefit can be obtained in partial-thickness burns, not full-thickness or third degree burn wounds. Flame burns seem to be benefiting less from HBO than scald burns, owing to the higher extent of direct tissue damage.

5. HBO protocol

Hyperbaric protocols are within standard pressure-time values for HBO: 2.0 to 2.5 ATA, for 90 minutes duration. Most clinical reports reporting favourable effects of HBO have a first treatment within a few hours after the burn wound, and administered two or even three HBO treatments within the first 24 hours. Treatment is usually continued for 3 to 7 days.

Fluid resuscitation protocols should be adapted to urinary output.
Vitamin E, Vitamin C or other anti-oxidants may be supplemented (63) (64).

Positive reports in clinical setting come from a small number of burn centres with motivated dedicated staff. These patients were all treated in monoplace chambers. Experimental studies on small UV-irradiated blister wounds were carried out in multiplace chambers. The only report of multiplace chamber HBO treatments for burn patients is underpowered and both groups are not comparable as to the origin of the burn, with a much higher proportion of flame burns in the HBO group (62). Another case series highlights the difficulties in managing severely ill intensive care patients without specifying any effect on the burn wound (54).

6. Cost impact

As the publications reporting the (direct) treatment costs are limited to one single burn centre, no conclusions can be drawn (59) (60). However, the cost of hyperbaric oxygen therapy should not be underestimated - in these studies, average cost of HBO reached more than 10 to even 20% of the total costs. Therefore, a significant effect of HBO must be anticipated in order to make this a cost-effective adjunctive treatment.

7. Discussion

The beneficial effects of HBO in the treatment of cutaneous burn injuries may seem evident, when examined from the animal experience. However, there is only limited consensus to formally accept "thermal burn" as an indication for HBO (65). The current evidence for HBO in burns apparently does not stand up to scrutiny for Evidence-Based Medicine (66). It is good to review the causes for this lack of evidence:

- Whereas in animal studies, standardised patients and burn wounds can be obtained relatively easily, this is much more difficult in the human setting: lack of uniformity of the burn wound, with areas of second and third degree, presence of other medical or surgical pathology, variable delay before treatment,… This makes the design of proper randomised prospective studies virtually impossible (65).
- The experimental endpoints, as defined in the experimental studies, are not easily transposed to clinical endpoints in the human trials. As an example, there is not one single undisputed objective measurement tool for determining the thickness of a burn wound; biopsies being only punctual, the clinical evaluation remains the most important but subjective evaluation tool (5).
- The integration of HBO in the early treatment of burn patients puts a high demand on the availability of the hyperbaric staff and a perfect integration with the burn care team. Any destabilisation, be it of a thermal, haemodynamic, nutritional or infectious nature, can easily disrupt and counterbalance the advantages obtained by HBO (67).
- For burn wounds of less than 20%TBSA, the advantage of HBO associated to the "classical" treatment will probably only be marginal. The risk of "distant" complications is low, and any excision of "third degree" burned zones will be easily covered by skin autografts. However, in the case of burns in aesthetically or functionally important zones (face, hands, perineum) or with precious vascularisation (cartilaginous – ears, nose) HBO might be considered.
- As HBO treatment will probably continue to be used only in major specialised burn centres, it is necessary to define as clearly as possible the different categories of patients for whom HBO is necessary. On the basis of current knowledge, only in the following conditions can HBO be expected to give a maximum benefit:
    - Patient selection: patients who will benefit most from HBO are those with a 20 to 50% TBSA, mixed second and third degree. More severely burnt patients have a higher risk of haemodynamic and infectious complications and should only be considered when HBO can be optimally organised (see below)
    - Early application: the first HBO session should be given within 6 hours after the burn injury
    - HBO protocol: two sessions per day, at a pressure of 2.0-2.4 ATA, for the first 4 to 5 days only
    - Volume resuscitation: the volume of fluids administered should be calculated on the basis of urinary output from the 12th hour on, maintaining adequate diuresis, while preventing pulmonary overload and taking into account the evolution of the patient's body weight
    - Treatment chamber: a "roll-in" multiplace chamber equipped for intensive care treatments, preferably with a (as good as possible) bacteriologic isolation, is preferred as this would minimise the risk of haemodynamic destabilisation. In this type of chamber the patient can be treated while on his own intensive care bed (without the need to use a special stretcher),

can be mechanically ventilated if necessary, and a continuous invasive monitoring of haemodynamic parameters is possible. Finally, any necessary perfusion type (pressure pump, free flow device) can be initiated without difficulty, even during the treatment session.

To this day, there is still a cruel lack of clinical studies that demonstrate unequivocally the benefits of investing in a difficult and costly therapy like HBO for the severe burn patient. Very few studies have been conducted in the last decades, lowering the weight of the available evidence.
At least one randomised prospective study should be initiated, more if possible. They should aim at evaluating short-term parameters, such as weight loss, necessary resuscitation fluid volumes, surface to be grafted, number of surgical interventions needed, length of hospital stay; but also long-term or indirect parameters: time to complete healing, time to return to "normal" or functional life,… These studies should only be conducted in burn centres that have a HBO centre either integrated in their infrastructure or functionally linked to it and available in their immediate (same building) neighbourhood – not in more "distant" HBO centres. In case multicentre studies are considered, these should at least also standardise the use of local dressings and ointments. Furthermore, a comparison with recently developed therapies (such as NWPT) could be useful.
For burns, even more than for any other of its applications, HBO therapy should be applied optimally, or not at all.

8. Conclusion : Recommendations and suggestions

1. We recommend that only highly specialised HBO centres, in the immediate vicinity of a burn centre, treat burns as an adjunct to classical burn care, taking care of optimal monitoring and fluid management. *Type 1 Recommendation, Level A Evidence*
2. We suggest that the most benefit can be obtained in severely scald burn patients (more than 20% TBSA), with a large surface of partial-thickness burns. *Type 2 Recommendation, Level C Evidence*
3. We suggest that burns to face (ear, nose), neck, hands and fingers and perineum may benefit even if the total surface burned is less than 20%. *Type 2 Recommendation, Level C Evidence*
4. We suggest that HBO be initiated within 6 (at the most 8) hours after the burn injury, and that two sessions per day (at a pressure of 2.0 to 2.4 ATA) be given for a minimum of three days. *Type 2 Recommendation, Level C Evidence*
5. We recommend that a (multicentre) study be initiated according to these parameters. *Type 1 Recommendation, Level A Evidence*

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Figure 1. Literature Search

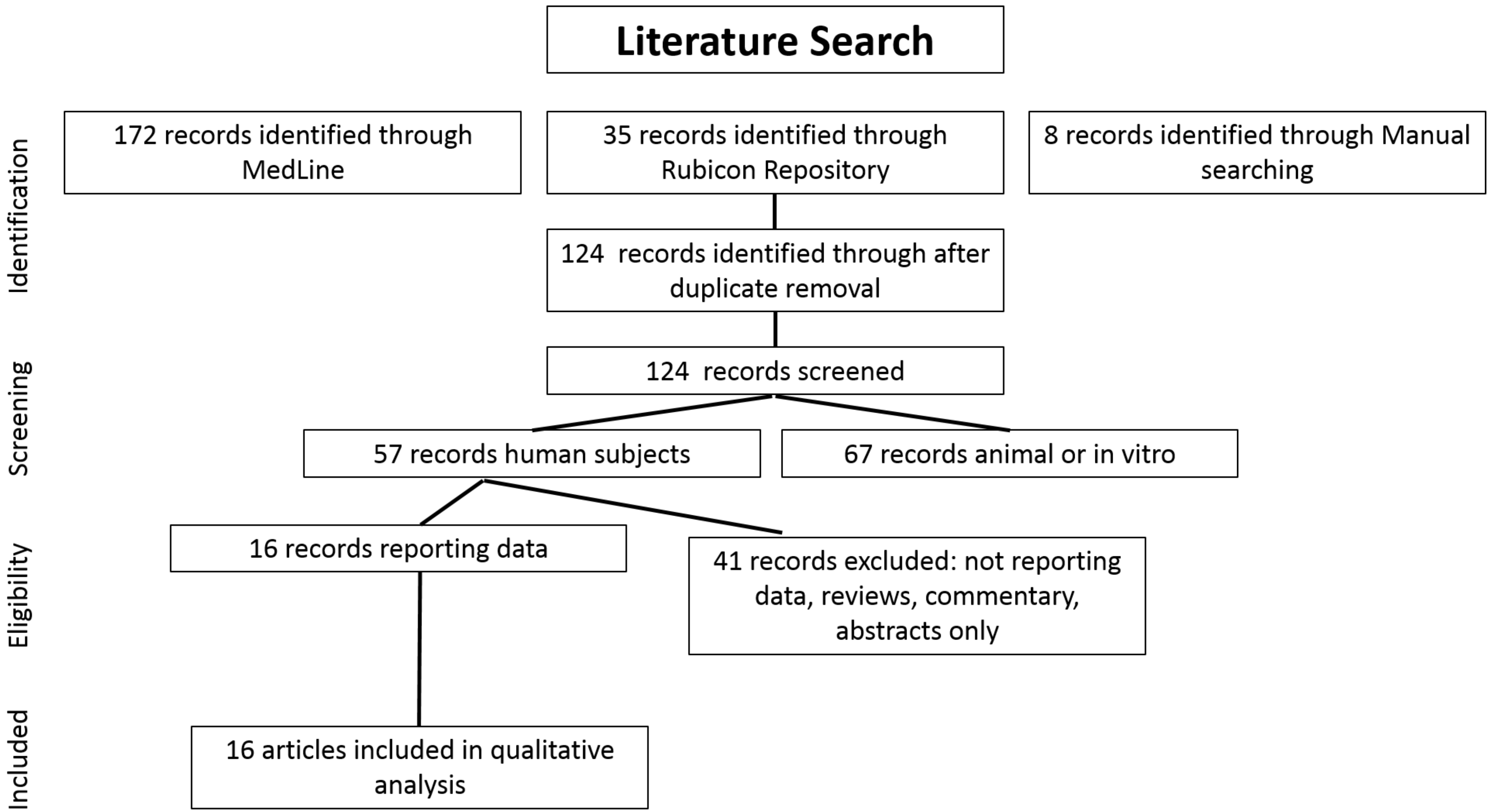

Table 1. Evidence base (human studies) HBO in the treatment of burns

Study (authors, year)	Type	Nb patients	Aim(s) / Evaluation criteria	Inclusion / Exclusion criteria	HBO protocol (pressure, time, nb of session)	Results	Conclusion / comment
Hart (Surg Gynecol Obstetr 1974) (47)	Prospective randomised, sham controlled double blinded study	16 (8 ctrl, 8 HBO)	- grafting need - fluid requirements - infection rate - healing time	4 paired groups of 2x2 patients, stratified according to TBSA (10-20, 20-30, 30-40, 40-50%)	- monoplace chamber - 2.0 ATA 90 minutes, 3x 1st 24Hrs; 2x next days until healing	- grafting: NS - fluids: 2.2 vs 3.4 ml/kg/% - infection: NS - healing time: 19.7 vs 43.8 days (accelerated healing regardless of %TBSA)	- no indication as to burn depth, however, patients were paired for severity - sham compression on air, blinded patient and physician - small sample - moderate/high level of evidence
Hart (Surg Gynecol Obstetr 1974) (47)	Retrospective, non systematic report	191 (53 non-HBO, 138 HBO)	- mortality rate	- inclusion: all burn patients prospectively evaluated for HBO - exclusion: >24 hours after burn, untreated neoplasma, pneumothorax, claustrophobia	- monoplace chamber - 2.0 ATA 90 minutes, 3x 1st 24Hrs; 2x next days until healing	- non HBO treated group 9% less mortality than national average, HBO 30-40% less mortality - less infection, Curling ulcus, hypertrophic scarring	- except for mortality rates comparison (HBO - no HBO - Am.Burn Association estimated), no other comparative data given, only impressions - moderate/low level of evidence
Grossman (Ann Plast Surg 1978) (48)	Retrospective , non systematic study	381 (243 Ctrl - 138 HBO)	- mortality rate - fluid requirements - duration of- duration of hospital stay	Excluded - Respirator dependent patients, obesitas (chamber fit)	- monoplace chamber - 2.5 ATA, 90minutes, 2 (<50% TBSA) or 3 times (>50% TBSA) per day, 7 days, ideally within 4 hours of admission	- mortality vs estimated mortality: 40% less (HBO), 13% less (non-HBO); 20-10% (HBO vs non-HBO historical data) - fluid requirements: 25-30% reduction (no data given) - hospital stay: 20-30% reduction HBO vs non HBO; - healing time for donor sites reduced (subjective)	- data for hospital stay compared with national burn association statistics - mortality data compared with own data from period 2 years earlier (1971-1972 vs 1973-1974) - HBO selection (partially) based on severity of patients (respirator, fractures, claustrophobia) - report emphasises the importance of competent staff - moderate/low level of evidence

Waisbren (Burns 1982) (55)	Retrospective paired control study	72 (36 Ctrl - 36 HBO)	- mortality rate - duration of hospital stay - infection rate	- inclusion: not specified - exclusion: not specified - selection of HBO and control patients based on blinded patient list with age and %TBSA as parameters	- monoplace chamber - "same protocol as Grossman and Hart"	- no increased mortality - no difference in hospital stay - decreased leucocyte counts and increased sepsis - increased renal failure	- in preliminary study, increased mortality found: this was not confirmed in this study - severe burns with high % FT (average 30% FT burn for 50+% TBSA) - reduced need for skin grafting (HBO 30% of non-HBO group) (no statistical analysis performed) - study has been criticized for having systematically administered nephrotoxic antibiotics - moderate/high level of evidence
Niu (J Hyperb Med 1987) (49)	Retrospective study	875 (609 Ctrl – 266 HBO)	- mortality rate - duration of hospital stay - fluid resuscitation	- inclusion: all burn patients; HBO given according to surgeon personal preference - exclusion: surgeon refusal, transfer delays (not further specified), contraindications for HBO, sepsis, unstable patients	- multiplace, oxygen filled chamber above "wet pot"; - 2.5 ATA, 90-120 minutes, 2-3 times in 1st 24hrs, 1-2 times/day afterwards. Total number of sessions not given (more than 2)	- mortality significantly decreased in high-risk burn patients (35-70 %TBSA, 15-45 years old): 6.8% vs 14.8% (p=0.028) - decreased length of hospital stay in high-risk patients (47 vs 59 days, NS) - fluid requirement decreased by 30-35% (no data given) - early nasogastric feeding possible	- large series, uncontrolled - HBO protocol not always followed -moderate/low level of evidence
Grube (J Burn Care Rehab 1988) (54)	Case series	10	Report of complications during HBO	CO intoxication + burns	- multiplace chamber in other building of hospital - HBO protocol: 5 hours duration, starting at 3 ATA	- severe complications in almost all patients - hypovolemia in 30%, respiratory acidosis in 40%; aspiration in 20% - other complications probably secondary to these	- 10 patients in 5 years - no information on severity or extent of burns - most complications related to transport & hemodynamic instability - no evaluation of effect on burns performed - reflects difficulties in managing intensive care HBO rather than lack of effect of HBO - low level of evidence

Gorman (SPUMS J 1988) (57)	Prospective study, retrospective control group	180 (113 Ctrl - 67 HBO	- mortality rate - complications (feasibility study)	- inclusion: all burn patients with TBSA 10-75% in a 2 year period included - exclusion: not specified	Multiplace, HBO protocol not specified	- decreased mortality (4.4% vs 21.3%) (p=0.002)	- retrospective control group from 3 years before HBO - HBO and ctrl groups similar regarding age, %TBSA - no severe complications (feasibility study) - moderate/low level of evidence
Cianci J Burn Care Rehab 1989) (59)	Retrospective, non systematic trial	20 (8 HBO - 12 Ctrl)	- length of hospital stay - total cost of care	- inclusion: all burn patients with TBSA 18-39% in a 5 year period - exclusion: non-availability of HBO chamber	- monoplace chamber - 2.0 ATA 90min, 2x/day	- decreased length of stay - no increase of costs	- 20-35 %TBSA - average 5% full thickness - small population over 5 year period : other selection of patients ? - moderate/low level of evidence
Lee (Zhongua Yi 1989) (58)	Retrospective report over 11 years' HBO activity (abstract only, article in Chinese)	not specified	- mortality rate	- inclusion: TBSA 35-70%, 15-45 years old - exclusion: not specified	not specified	- reduced mortality rate (6.8% vs 14.8%) ("p<0.05")	- low level of evidence
Cianci (J Burn Care Rehab 1990) (60)	Retrospective, non systematic case-control study	21 (11 Ctrl - 10 HBO)	- length of hospital stay - number of surgical interventions - total cost of care	- inclusion: all burn patients TBSA 19-50% - exclusion criteria: not given - patients matched for age, TBSA, %FT burn	- monoplace chamber - 2.0 ATA 90min 2x/day	- reduced length of hospital stay 35% reduced - 39% less surgery procedures - cost savings 31.600$/pt (35%)	- only 21 patients in 5 years ? - moderate/high level of evidence
Hammarlund (Burns 1991) (45)	Prospective, non blinded study	7 (7 vs 7) same subjects sequentially	- wound hyperemia - wound exsudation	- intervention: standardised experimental burn wound (suction / UV-radiation) (TBSA <1%)	- 2.83 ATA 60min - multiplace chamber - 3 sessions in 24 Hrs, starting 1.5 hours after wound	- reduced wound hyperemia and oedema by 40% - exsudation reduced by 49%	- small wound, early treatment - moderate/high level of evidence
Niezgoda (Plast Reconstr Surg 1997) (46)	Randomised, placebo controlled blinded trial	12 (6 Ctrl - 6 HBO)	- wound hyperemia - wound exsudation	- intervention: standardised experimental burn wound (suction / UV-radiation) (TBSA <1%)	- 2.4 ATA - multiplace chamber - 2x/day 3 days, starting 2 hours after wound - sham 8.75% O2 /2.4 ATA)	- wound hyperemia 42% reduction - wound size 35% reduction - exsudation 22% reduction	- small wound, early treatment - moderate/high level of evidence

Brannen (Am Surg 1997) (56)	Retrospective controlled study, no placebo treatment	125	- mortality - number of operations - length of hospital stay	- inclusion: admission <24hrs after burn, HBO chamber availability - control patients matched by burn size, age, presence of inhalation injury	- monoplace chamber - 2.0 ATA 90min - 2x/day minimum 10 sessions, max 1 HBO per %TBSA	- no significant differences in primary outcome parameters - report of less fluid loss and faster healing, no data given	- HBO given not before 8th hour post-burn - study has been criticized for very aggressive excision strategy - moderate/high level of evidence
Xu (Zhonghua Zheng 1999) (52)	Prospective randomised trial (abstract only, article in Chinese)	42 (17 Ctrl - 25 HBO)	- serum Interleukin Receptor levels - serum Fibronectin levels - incidence of sepsis	- inclusion: >30% TBSA; 3rd degree >10% - exclusion: not specified	not specified in abstract	- reduction of ILR - increase of Fn - reduction of sepsis (all significant)	- time to first HBO not specified - randomisation not specified; unequal groups - moderate/low level of evidence
Kemmer (Proc EUBS Meeting 1999) (50)	Case series	16	- oedema - healing time - complications and difficulties (feasibility study)	- inclusion: not specified; most had facial burns - exclusion: not specified	- multiplace chamber - 2.4 ATA, 90 minutes - 2/day 1st day, then 1/day	- less general oedema especially in face and hand burns - faster healing in 2nd degree facial burns - risk of fluid overloading if calculated amount is not reduced	- no (comparative) data given - report emphasises the importance of competent HBO staff and equipment, as well as cooperation with burn specialists - low level of evidence
Chong (Diving Hyperb Med 2013) (62)	Prospective, randomised, non blinded study	17 (9 Ctrl - 8 HBO)	- evolution of burn depth (Laser Doppler Imaging) - white blood cell count and positive cultures - serum interleukin (IL) level	- inclusion: <40 %TBSA, admission within 24hrs of burn - exclusion: any comorbidities, intubated patients	- 243 kPa 90 mins - multiplace chamber - two sessions within 22Hrs of admission - 1st HBO 24-48 Hrs after injury	- no significant changes in burn depth and IL; - tendency to have less infection	- Small study; recruitment difficulties (Power calculation: 40 in each group: not attained) as only 18 of 110 patients fulfilled inclusion/exclusion criteria - small burns (13 % and 12%TBSA resp.) - higher proportion of flame burns in HBO group (5/8 vs 2/9) - burn depth expressed only as Deep or Superficial – no indication of surface area of each - only two HBO sessions given - time to first HBO not specified - moderate/low level of evidence