DELAYED TREATMENT OF BUBBLE RELATED ILLNESSES IN DIVING – REVIEW OF STANDARD

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"*The treatment of decompression sickness is more than turning a valve and applying pressure*"
Eric P. Kindwall, 1973

ABSTRACT

The basic treatment of diver with bubble related illness consists of recompression in medical hyperbaric facility. However transportation of injured diver to hyperbaric chamber can last for several hours. During that time the process induced by gas bubbles spread out and finally result in activation of many pathophysiological events. Currently approved standard of treatment before starting of recompression consists of normobaric oxygenation, intravenous or oral fluids and general stabilization of the patient condition. Usage of several pharmacological agents is promising, including corticosteroids, antiplatelet and anticoagulant therapy or lidocaine. Those drugs are most often used in some centres but still there is lack of randomized controlled studies concerning their efficacy in decompression illness of divers. The review of available bibliography presented in this paper leads to conclusion that recommendations of the Second European Consensus Conference on Hyperbaric Medicine "The Treatment of Decompression Accidents in Recreational Diving" published in 1996 in Marseille, France for fluid replacement and drug therapy for decompression accidents are still valid. This protocol includes the fluid treatment, normobaric oxygen and intensive therapy. Other drugs (aspirin, lidocaine, heparin, steroids, calcium channel blockers, antioxidants) should still be treated as an option considered by clinician, but without strong evidences from clinical studies.

INTRODUCTION

Regardless of increasing number of hyperbaric chambers installed in different places, diving accidents with bubble related illness (decompression illness, DCI) may occur in areas from which transportation to recompression chamber can last for more than 6 hours. As time passes, the pathophysiological events induced by gas bubbles change significantly the course of the disease and different abnormalities, not necessarily present at the time of accident, can become clinically important, including endothelial and complement activation, inflammation reactions and disorders of coagulation system. Up to now the standard of treatment of DCI consists of recompression (sometimes with repeated sessions), normobaric oxygenation until the time of hyperbaric therapy, intravenous or oral fluids and general stabilization of patient condition. There is no treatment specific

for DCI with clinical value established on evidence based medicine, other than recompression. However some treatment modalities are being proposed since many years, including corticosteroids, anticoagulants, neuroprotective drugs and others. In 1996 the Second European Consensus Conference on Hyperbaric Medicine "The Treatment of Decompression Accidents in Recreational Diving" was held in 1996 in Marseille, France [50]. It recommended the protocol for fluid replacement and drug therapy for decompression accidents. This protocol includes the fluid treatment (strongly recommended), normobaric oxygen (strongly recommended), intensive therapy (recommended), and optional drugs (aspirin, lidocaine, heparin, steroids, calcium channel blockers, antioxidants) to be considered by clinician. The aim of this paper was to review the literature in order to check if the existing standard of treatment of DCI needs change which could be scientifically reasonable.

DELAY TO TREATMENT

The delay of more than 6 hours to receive the recompression treatment after the diving-related accidents is not unusual in recreational and professional diving. Of 382 cases of DCI reported in the 2002 DAN Report only 23% received recompression therapy within 6 hours of the onset of symptoms, and only 54% within first 24 hours [1]. This delay can depend on several factors including: 1) delay in occurrence or recognizing the symptoms, 2) delay in getting hyperbaric advice and 3) delay in transportation (remote locations).

The delay in occurrence of symptoms depends on type and severity of diving accident. Symptoms involving central nervous system (CNS) usually warn divers early. In retrospective study Francis et al collected from literature 1070 human cases with DCI involving the cerebrum, spinal cord, and both [2]. They showed that half of all cases became symptomatic only about 8 minutes after returning to 1 ata (3 minutes for cerebral DCI comparing to 9 minutes for spinal cord DCI), and only about 15% presented more that 1 h after surfacing. In 117 cases of arterial gas embolism (AGE) referred to the Institute of Naval Medicine (UK) the onset times were generally within 5 min of surfacing (83% of cases), and surprisingly high number of symptoms occurred while still at pressure (9% of cases) [3]. However the delay in occurrence (or recognizing) of symptoms can be long even after CNS DCI. In 28% of 50 cases reported by Van Hulst [4] and 21% of 24 cases reported by Kiser [5] the time of the onset of symptoms was more than 6 hours.

The delay in getting hyperbaric advice and the delay in transportation from remote locations can be surprisingly long even for relatively short distance. Desola reported more than 18 hours of mean time between the onset of symptoms and the arrival of the patient to the hyperbaric center (48% of cases in more than 6 hours), despite the fact that the longest distant from diving sites in this area was for maximum of 3 hrs of transportation [6].

Many authors noted the inverse relationship of delay and probability of complete or partial relief of symptoms in bubble related disorders (DCI, AGE) – Tab. 1. The effectiveness of treatment in "short" delay presented there is close to generally accepted 81% of success rate of a single recompression using USN oxygen treatment tables [7], and significantly decreases with "long" delays.

Tab. 1. Rate of complete relief of symptoms in relation to delay from the onset to the recompression treatment.

REFERENCE	"SHORT" DELAY	"LONG" DELAY
Decompression illness		
[8]	0÷24 hrs – 51/79 (65%)	25÷96 hrs – 67/126 (53%)
[7]	NR[1]	"Long delay" – 91/157 (58%)
[7]	NR[1]	"Mean delay 48 h" – 29/58 (50%)
[5]	0÷12 hrs – 10/13 (84%)	12÷24 hrs – 7/13 (54%)
[4]	0÷12 hrs – 24/30 (80%)	12+ hrs – 11/20 (55%)
[9]	0÷12 hrs - NR[1] (66%)	24+ hrs – 12/24 (50%)
[10]	NR[1]	"97% cases 24+ hrs" – 22/51 (43%)
Pooled[2]	**85/122 (70%)**	**239/449 (53%)**
Iatrogenic air embolism		
[11]	0÷5 hrs – 6/9 (67%)	5+ hrs – 2/6 (33%)
[12]	0÷6 hrs – 7/9 (78%)	6+ hrs – 1/8 (12%)
[13]	0÷6 hrs – 2/3 (67%)	6+ hrs – 7/11 (64%)
[14]	0÷5 hrs – 5/8 (63%)	5+ hrs – 2/6 (33%)
[15]	0÷4 hrs – 50/64 (78%)	4+ hrs – 20/46 (44%)
[16]	0÷3 hrs – 9/9 (100%)	NR[1]
Pooled[2]	**79/102 (77%)**	**32/77 (42%)**

[1] Not reported
[2] p<0,001, two-sided chi-square test

However, such significant influence of delay of treatment on final outcome has not been observed in more recent analyses [17]. Desola et al in a multivariate analysis of 554 cases did not find a delay from onset of symptoms to recompression treatment to be an independent predictor of outcome [18, 19]. In this study only age, gender and hematological parameters (hematocrit and fibrinogen degradation products level) were identified as prognostic factors for worse outcome. Therefore the relation between the delay to treatment and prognosis for outcome still remains a controversial issue.

THERAPEUTIC OPTIONS

Recompression

If used immediately after the bubbles are created the recompression can be the only procedure necessary to stop the pathophysiological creation of decompression illness [25, 28]. Surface decompression procedure, used extensively by many military and professional divers, gives evidence that there is a therapeutic window before consequences of gas bubble occur. In DCI delay in recompression shorter than 8 to 10 min may result in minimal activation of tissue reactions, and secondary bubble effects may not have time to develop to a clinically significant degree, with the exception of blow-ups from extreme depths, when symptoms can occur even at depth [25]. Clinical observations confirm that pressure is effective if used immediately, and can lead to rapid, complete recovery after gas embolism [21, 29].

These observations promoted usage of in-water recompression (especially with oxygen) in situations when transportation to hyperbaric center in not possible or would result in unacceptable long delays (remote locations). In-water recompression is overweighting the obvious drawbacks (immersion, dehydration, hypothermia, gas toxicity, etc.) by instant application of pressure. There are

a lot of case observations supporting the value of this procedure, and it is discussed in details by Edmonds [30]. However, in any circumstances it should not be treated as an alternative to the recompression treatment in hyperbaric chamber, nor should it delay the transportation to the hyperbaric center. It is dedicated for special applications only [US Navy Diving Manual, 31] and it is not recommended for recreational diving [32].

In any case of DCI the recompression in the hyperbaric chamber should be treated as a basic therapeutic option, therefore injured diver should be referred to the hyperbaric center using fastest medical evacuation mode. However the maximum delay which is still worth to do recompression has not been established yet. Pooled data from DCI reports (Table 1) shows positive effects of recompression treatment still in 53% of cases with "long-delay". Reports by several authors and data from larger series suggest the benefit of hyperbaric treatment for divers with decompression illness up to ten days after the onset of symptoms [33, 34, 35]. Myers reported 3 cases of divers with DCI treated successfully by HBO after 3, 5 and 7 days [36]. Massey reported cases of iatrogenic air embolism treated successfully with HBO after 24, 31 and 42 hours [13]. The presence of air bubbles in the intravascular space was reported for more than 48 hours after an air ambolism [37], and free gas phase was diagnosed even after 10 days by MRI in spinal cord DCI [38]. Therefore, in any case of DCI regardless of delay the symptomatic patient should be referred to the hyperbaric center for recompression treatment.

Hyperbaric / normobaric oxygen

With the exception of immediate recompression treatment of cases with relatively small gas burden when the increasing of pressure can effectively cure the decompression illness by itself, the effective treatment of diving-related accidents should apply measures to prevent or treat the secondary effects of gas bubbles. This deserves special attention mainly during delay to recompression treatment (diving in remote locations). After clinically significant bubbles are generated the first most important step is to stop the ischemia. This should be preferably done by application of hyperbaric oxygen (HBO), but – if HBO is not available - normobaric oxygen should be administered as soon as possible at the maximum concentration available (preferably 100% using non-rebreathing masks). The evidences for usage of normobaric oxygen come from retrospective observations, mainly published annually by DAN. In 402 cases with DCI reported to DAN between 1989-1996 forty six percent was transported to the hyperbaric chamber with Oxygen First Aid (OFA), and other 54% without it [39]. In the group without OFA ninety six percent of injured divers arrived to the HBO center in stable condition or worsened, 3% arrived with significant improvements and only less than 1% of them were symptom free. In comparison, only 39% of injured divers transported with OFA were stable or worsened on admission, 45% had significant improvement, and almost 16% were symptom free. The efficacy of normobaric oxygen was also clearly shown in animal research concerning removal rate of air from cerebral arteries of dogs [40] and pigs [41] ventilated with 100% of oxygen after AGE and elimination of circulating venous bubbles in goats by breathing of 100% of oxygen after submarine escape simulation [42]. Regardless of good evidence for usage of normobaric

oxygen in DCI, it can not eliminate the need for pressurization for DCI [41], therefore it is recommended as a standard treatment during transportation.

Fluids

Increased permeability of damaged endothelium causes the loss of intravascular fluids, and this is mediated probably by prostaglandins, as indomethacin given prophylactically in animals inhibits these losses [43]. This change in body fluids has additive effect to dehydration frequently seen in divers, due to immersion and hypo- or hyperthermia. Brunner observed 20% or more of plasma volume losses in two human dysbarism [44], and this was confirmed in observations of dysbarism in animals, when losses of about 25 to 40% of plasma volume were noted [20, 43]. In case of neurological DCI the blood flow in the CNS strongly depends on blood pressure, as autoregulation is inhibited [22, 23, 24]. Therefore any significant loss of intravascular fluids can lead to neurological deterioration, and this was confirmed in observational study of Blanc at al [45], where high hematocrit level (more than 48%) was significantly correlated with the presence of neurological sequelae (53% vs 13% in 58 divers). The strong need for rehydration of divers with DCI is well recognized, however the type of fluid used is still controversial. The only research concerning this problem directly for decompression illness was conducted using goats [46]. Comparison of Dextran 40, Dextran 70, 10% glucose, lactated Ringer's solution, and 10% mannitol resulted in following conclusions: 1) all fluids tended to reduce the severity of signs of DCI, 2) mannitol and Dextran 40 produced significantly better responses that the others, 3) animals that did not develop arterial bubbles responded better to fluid therapy than those that did develop bubbles, and 4) treatment with any of the five plasma volume expanders tended to decrease the number of arterial bubbles. Mannitol is not infrequently used as an adjunctive drug in the treatment of severe DCI [47], and in one case report was used in neurological DCI successfully treated without recompression [48]. Searching for evidence for using of mannitol in acute ischemic stroke shows that there is currently not enough evidence to decide whether the routine use of mannitol would result in any beneficial or harmful effect [49]. On the other hand mannitol therapy for raised intracranial pressure (ICP) in patients with brain injury may have beneficial effect on mortality when compared to other drugs (pentobarbital), however there are insufficient data on the effectiveness of pre-hospital administration of it to preclude either a harmful or a beneficial effect on mortality [49]. This evidence supports the restriction of using mannitol to control ICP only in hospital environment. Regardless of superiority of Dextran 40 in animal DCI there is no evidence from randomized controlled trials that resuscitation of patients trauma, burns and following surgery with colloids reduces the risk of death compared to crystalloids [50], and there is no evidence that one colloid solution is more effective or safe than any other, although the confidence intervals are wide and do not exclude clinically significant differences between colloids [51]. It has to be remembered that those analyses are concerning critically ill patients not involved in diving-related accidents, but this is the only clinical data available yet. Dextrose infusion or increases plasma glucose resulted in significantly greater cerebral injury at 96 hours postischemia when comparing both neurological and histopathological scores after complete cerebral ischemia in primates [52], and

worsened neurological outcome after spinal cord ischemia in rabbits [53]. The multivariate analysis of National Institute of Neurological Disorders and Stroke recombinant tissue plasminogen activator Stroke Trial data of 624 patients after acute ischemic stroke concluded that higher admission glucose levels are associated with significantly lower odds for desirable clinical outcomes and significantly higher odds for symptomatic intracerebral hemorrhage, regardless of recombinant plasminogen activator treatment [54, 55]. Also in patients with head injury it was shown that hyperglycemia on admission is a significant indicator of severity of injury and a potent predictor of the outcome from head injury [56, 57, 58]. All those evidences suggest avoiding dextrose infusions in CNS DCI, however they are drawn from non-diving related medical conditions.

Drugs

The nature of secondary effects of gas emboli suggests that adjunctive drug therapy may become more important when compression therapy with hyperoxygenation is delayed [59]. There have been many drugs proposed to be useful in treatment of DCI, however none of them has been tested in randomized controlled trial (RCT) with placebo group – the gold standard of trials currently accepted in clinical sciences. Evidences for their application in human DCI can be only drawn from retrospective non-controlled studies and case reports. The alternative way is to use the results of the RCTs for pathologies which lead to same secondary effects as intravascular bubbles. In this paper RCTs for stroke, and brain and spinal cord injury are referenced.

Corticosteroids

There is no RCT on steroids in DCI. The positive affects of corticosteroids in treatment of DCI has been observed in many reported single cases usually given with other drugs [29, 34, 59, 60, 61, 62, 63, 65, 66]. Kizer reported that the complete recovery from AGE or neurological DCI was observed in 10 of 12 (84%) of patients treated with steroids as compared to 7 of 13 (54%) patient treated without steroids [5]. In Leitch et al paper [3] none of 18 (20%) with relapse after treatment of AGE treated with signs and symptoms received prophylactic steroids while 33 (37%) other cases receiving steroids did not relapse. Seven of the relapses were given steroids after the event and had no further relapse after recompression. Also Pearson et all noted that of 37 patients with cerebral AGE with dexamethasone 4 patients (11%) relapsed, in contrast to 95 patients without dexamethasone, among whom 28 patients (29.5%) relapsed [60].

A review of randomized trials concerning acute spinal cord injury [67, 68, 69, 70] showed that corticosteroid therapy (with high dose methylprednisolone steroid) is the only pharmacological therapy shown to have efficacy in a Phase Three randomized trial when it can be administered within eight hours. A recent trial indicates additional benefit by extending the maintenance dose from 24 to 48 hours if start of treatment must be delayed to between three and eight hours after injury [70]. However the level of significance of this research is nowadays questioned and after the critical appraisal the Canadian Association of Emergency Physicians lowered the evidence level from treatment standard to a treatment option [71].

On the other hand the meta-analysis [72] of 19 trials with 2295 patients with acute traumatic brain injury randomized to receive corticosteroids lead to conclusion that neither moderate benefits nor moderate harmful effects of steroids can be excluded. Aggregate mortality results from 13 RTs of steroids in head injury [73] shows reduction of mortality from 39% in controls to 37% in steroid-treated (N=2147), which means that the absolute benefit of steroids (if any) is 2%, indicating 1 death prevented for every 50 patients treated. This weak effect can be explained by showing that in RCT concerning corticosteroids (dexamethasone) in severe head injury 90% of all deaths were caused by recurrent intracranial hematomas, medical complications, or diffuse brain injuries with parenchymal hemorrhage and tissue disruption – causes of death which cannot be affected by corticosteroid therapy [74].

Analysis of the effect of corticosteroids in acute presumed ischaemic stroke [75] showed that there is not enough evidence to evaluate corticosteroid treatment in those cases, as no difference was shown in the odds of death within one year in pooled seven randomized controlled trials involving 453 cases.

Nevertheless the therapeutic time window of steroids is narrow and the effect of steroids depends on the interval between injury and initiation of its administration [76]. Therefore if it is decided to use steroids they should be administered as soon as possible after the insult.

Antiplatelet therapy - Aspirin

There is no RCT concerning use of aspirin in DCI patients, however there are some case reports confirming its efficacy, at least if given with other drugs [34, 59].

The efficacy of aspirin to reduce the risk of early recurrent ischemic stroke was shown in review of 8 randomized trials involving 41,325 patients [77]. It has been concluded that antiplatelet therapy with aspirin 160 to 300 mg daily, given orally (or per rectum in patients who cannot swallow), and started within 48 hours of onset of presumed ischemic stroke reduces the risk of early recurrent ischaemic stroke without a major risk of early hemorrhagic complications and improves long-term outcome.

Anticoagulant therapy - Heparin

There is no RCT concerning use of anticoagulants in DCI patients, however there are some case reports confirming efficacy of heparin, at least if given with other drugs [26, 48, 60, 61, 63, 64, 78].

The results of animal studies are confusing [79], as some of them did not support the prophylactic or therapeutic use of it in DCI [80, 81], some other did [27, 64, 82, 83, 84].

The effect of anticoagulant therapy (standard unfractionated heparin, low molecular weight heparins, heparinoids, oral anticoagulants, and thrombin inhibitors) in the early treatment of patients with acute ischaemic stroke was assessed in analysis of 22 randomized trials involving 23,427 patients [85]. It was concluded that immediate anticoagulant therapy in patients with acute ischaemic stroke is not associated with net short- or long-term benefit and that data from this review do not support the

routine use of any type of anticoagulant in acute ischaemic stroke. Another review of 4 randomized trials with a total of 16,558 patients was performed to assess: 1) effectiveness of anticoagulants compared with antiplatelet agents in acute ischaemic stroke and 2) whether the addition of anticoagulants to antiplatelet agents offers any net advantage over antiplatelet agents alone [86]. This review concluded that anticoagulants offered no net advantages over antiplatelet agents in acute ischaemic stroke. However the combination of low-dose unfractionated heparin and aspirin appeared in a subgroup analysis to be associated with net benefits compared with aspirin alone, and this merits further research.

Lidocaine

There is no RCT to support uses of lidocaine in DCI, however lidocaine has been reported in treatment of DCI [29, 87], including case report of diver with unsuccessful recompression treatment later resolved by lidocaine infusion [88, 89]. Mutzbauer et al reported compared 9 cases with DCI treated lidocaine and HBO to the historical control group treated by HBO without lidocaine and concluded than less HBO and time breathing oxygen under hyperbaric conditions were needed in lidocaine group [90].

The positive effect of lidocaine was also noted in animal research. The data from research of CAGE in cats suggests that lidocaine administration facilitates the return of neural function (measured by spinal evoked potentials) [81]. This was partially confirmed by study by McDermott et al when both HBO and the combination of HBO and lidocaine (in cerebral AGE in cats) promoted a significant recovery of the SEP amplitude compared to no treatment [92]. However, in this research lidocaine therapy added no benefit to HBO therapy alone. Also Dutka did report a significant benefit in adding lidocaine to HBO in dogs subjected to carotid artery bubbles, where animals who received HBO plus lidocaine recovered more spinal evoked potentials amplitude than those treated with HBO alone (60 vs 28%) [88].

There is a report of a strong and persistent cerebral protective effect of lidocaine which was unrelated to any effect on depression or anxiety, and was at a level that was noticed by the patients in a randomized, prospective, double-blind trial in cerebral outcome after left heart valve operations which has a high risk of perioperative brain injury [87].

In a critical appraisal of usage of lidocaine in DCI Mitchell reviewed the literature and concluded that there is "*sufficient evidence to justify prophylactic lidocaine administration in clinical settings where CAGE is invariable or highly likely, such as during open chamber left heart surgery (…) and there is a sufficient evidence (and sufficiently low risk) to justify expeditious therapeutic lidocaine administration in patients or divers suffering unequivocal cerebral AGE (…) and there is insufficient evidence upon which to base a recommendation for lidocaine administration in DCI that does no appear to involve CAGE*" [93].

Other drugs

Other types of drugs have been proposed or noticed as of possible specific use in DCI – nicotinic acid, antihistamines, bronchodilators, vasodilators, vasopressors, NSAIDs, NMDA blockers, perfluorocarbons, free radical scavengers, calcium channel antagonists, PARP inhibitors, GABA agonists, and others, however until now they have not been used in human research.

Relevance of the evidence to treatment of DCI

Up-to-date there is no RCT concerning drug therapy in DCI. Therefore the evidence for using each drug comes from retrospective data, case observations, animal research, and RCTs from "similar" medical conditions. However limitations of those data are self explanatory. Moreover, it must be acknowledged that in most relevant studies tested drugs were administered with a short delay from insult, and in some of them as a prophylactic treatment (given before the insult). Therefore extending the positive effects noted in research to treatment of delayed cases can result in significant difference of final outcomes.

CONCLUSIONS

From this paper it can be seen that no single drug should be treated as a standard of care for divers with bubble related illness before recompression treatment. In a pre-hospital phase only normobaric oxygen and rehydration (with avoiding glucose infusion unless hypoglycemia is being specifically treated) can be recommended as a standard. In a hospital phase a symptomatic approach (general stabilization of patient status) with continuation of normobaric oxygen and fluid therapy (with same note as above) can be recommended. All drugs which are proposed to be used in DCI have not been tested in a RCT yet, and there is no evidence to recommend them as a standard. To the knowledge of author only lidocaine are planned to be tested in DCI using RCT. The results of this trial, when published can change today's recommendations stated in the Second European Consensus Conference on Hyperbaric Medicine "The Treatment of Decompression Accidents in Recreational Diving" published in 1996 in Marseille, France [32]. The recommended protocol includes the fluid treatment (strongly recommended), normobaric oxygen (strongly recommended), intensive therapy (recommended), and optional drugs (aspirin, lidocaine, heparin, steroids, calcium channel blockers, antioxidants) to be considered by clinician. It is the opinion of author that up-to-date there is no data to significantly change the level of existing recommendations.

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