

A retrospective cohort study of lidocaine in divers with neurological decompression illness

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ABSTRACT

Lidocaine is the most extensively studied substance for adjuvant therapy in neurological decompression illness (DCI), but results have been conflicting. In this retrospective cohort study, we compared 14 patients who received adjuvant intravenous lidocaine for neurological decompression sickness and cerebral arterial gas embolism between 2001 and 2011 against 21 patients who were treated between 1996 and 2001 and did not receive lidocaine. All patients were treated with hyperbaric oxygen (HBO₂) therapy according to accepted guidelines.

Groups were comparable for all investigated confounding factors, except that significantly more control patients had made an unsafe dive (62% vs. 14%, $p = 0.007$). Groups had comparable injury

severity as measured by Dick and Massey score (lidocaine 2.7 ± 1.7 , control 2.0 ± 1.6), an adapted version of the Dick and Massey score, and the Blatteau score. Number of HBO₂ sessions given was comparable in both groups (lidocaine 2.7 ± 2.3 , control 2.0 ± 1.0). There was neither a positive nor a negative effect of lidocaine on outcome (relative risk for objective neurological signs at follow-up in the lidocaine group was 1.8, 95% CI 0.2-16).

This is the first retrospective cohort study of lidocaine in neurological DCI. Since our study is underpowered to draw definitive conclusions, a prospective multicenter study remains the only way to reliably determine the effect of lidocaine in neurological decompression illness.

INTRODUCTION

Neurological decompression illness (DCI) is one of the most serious complications of diving, at times resulting in mortality and permanent morbidity [1]. Neurological DCI encompasses two disease entities, neurological decompression sickness (DCS) and cerebral arterial gas embolism (CAGE). Although pathophysiology and clinical presentation of these two diseases are different, treatment for both conditions is the same and consists of prompt administration of 100% oxygen and intravenous fluids followed by expeditious administration of hyperbaric oxygen (HBO₂) therapy [2].

The search for adjuvant therapies to improve outcome in neurological DCI has led to the investigation of intravenous lidocaine as a neuroprotective agent. This sodium channel blocking and anti-inflammatory agent

has shown promising results in several animal studies [3,4], but subsequent animal and human investigations have yielded conflicting results [5-9]. Based on the positive effects of lidocaine reported in the literature, in 2001 the decision was made to apply intravenous lidocaine as adjuvant therapy in all cases of neurological DCI presenting to the Diving Medical Center of the Royal Netherlands Navy. In the present study, we report on the efficacy of lidocaine in our patients from 2001 to 2011, using an historic cohort as the control group.

METHODS

Standardized patient documentation was introduced at our institution in 1996. Adjuvant treatment with lidocaine in all patients with neurological DCI was

TABLE 1: Severity scores used in the study**A. Dick and Massey severity score** (total possible score is 10).

Sensory symptoms	1. paresthesia of single limb or area 2. paresthesia of multiple regions 3. numbness of single region or limb 4. numbness of two regions or limbs 5. numbness of three or more limbs
Motor symptoms	1. paresis of single limb or muscle group 2. paresis of multiple limbs or muscle groups 3. paralysis of single limb or muscle group 4. paralysis of two limbs 5. paralysis of three or more limbs

B. Adapted version of Dick and Massey severity score (total possible score is 24).

The following items are scored, giving 0 points for absence, 1 point for mild presence and 2 points for severe presence. This score is added to the Dick and Massey score as calculated in panel A.

Deep boring limb/abdominal pain, headache, vertigo, dyspnea, skinbends, visual disturbances, general malaise.

C. Blatteau severity score (total possible score is 22).

Age \geq 42	no = 0	yes = 1	
Back pain	no = 0	yes = 1	
Clinical course before recompression	better = 0	stable = 3	worse = 5
Objective sensory deficit	no = 0	yes = 4	
Motor impairment	no = 0	paresis = 4	paralysis = 5
Bladder dysfunction	no = 0	yes = 6	

A = Dick and Massey severity score [12]. **B** = adapted version of Dick and Massey severity score. **C** = Blatteau severity score [13].

introduced in June 2001. We reviewed all medical files of patients treated with HBO₂ therapy from 1996 to 2011 to include patients for our study. Included patients were those with a diagnosis of neurological DCI (neurological DCS or CAGE) who received U.S. Navy Treatment Table 6 as their first HBO₂ session at our institution within 72 hours after start of symptoms following a dive. Patients who were comatose on arrival were excluded. Since all patient information was handled anonymously, no informed consent was obtained from the patients.

From the included patient files we extracted sex, date of birth, weight, length, characteristics of the dive – duration, depth, breathing gas, diving in the preceding 18 hours (repetitive dive) – as well as time from end of dive to start of symptoms and time from start of symptoms to start of HBO₂ therapy.

Also, the dive performed was compared to the Canadian Defence and Civil Institute of Environmental Medicine dive tables and their guidelines [10,11] to see whether the required decompression stops were

adhered to. If not, or if the diver's dive computer indicated that decompression stops had been missed, the dive was categorized as unsafe. The dive was also classified as unsafe if the diver indicated that a rapid ascent had been made, the water had been cold ($< 15^{\circ}\text{C}$) or strenuous exercise had been performed during the dive.

Clinical course from start of symptoms to beginning of HBO₂ therapy was noted as improving, stable or worsening. Neurological symptoms were graded according to the Dick and Massey (DM) scoring system [12] (Table 1). We also calculated the severity score as devised by Blatteau [13] (Table 1, an adapted version of the original score introduced by Boussuges [14]). Since both these scores are primarily designed for use in spinal cord DCS, we furthermore calculated an adapted version of the DM scale to include symptoms specific for cerebral DCS, vestibular DCS and CAGE (Table 1). Diagnosis as established based on history and physical and neurological examination, in accordance with the U.S. Navy Diving Manual [15], was recorded.

As for treatment, we noted type and amount of HBO₂ treatments and whether or not lidocaine was given. Neurological symptoms at the end of the last HBO₂ session were noted, from which DM score as well as our adapted version of this score were calculated. Outcome after the last HBO₂ session was also expressed as absence or presence of objective neurological signs. Since follow-up data were available in only 14% of patients, we were not able to determine delayed outcome.

Patients suspected of neurological DCI (including those with only subjective symptoms) who are presented to our institution are immediately treated with 100% oxygen followed by neurological examination and initiation of U.S. Navy Treatment Table 6 as soon as possible. This table is extended if necessary as recommended in the U.S. Navy Diving Manual [16]. Additional treatment tables (U.S. Navy Treatment Table 5 or 6, HBO₂ at 1.9 atmospheres absolute (190 kPa) for 180 minutes or HBO₂ at 1.5 atmospheres absolute (150 kPa) for 90 minutes (at the diving medical officer's discretion) are prescribed when residual symptoms are present. 24-hour intervals are maintained between HBO₂ sessions. Administration of additional HBO₂ sessions is stopped when no further improvement is observed or the patient reports symptoms of pulmonary oxygen toxicity.

Adjuvant treatment with intravenous lidocaine (implemented in June 2001) consists of an initial bolus of 100 mg at the start of the first HBO₂ therapy session followed by continuous administration of 3 mg/minute over eight hours.

Statistical analysis was performed using SPSS version 17.0 (SPSS Inc., Chicago, Ill.). Differences for nominal variables between control and lidocaine groups were tested using Fisher's exact test for 2x2 tables and Chi-Square test (without continuity correction) for 2x3 tables. Chi-Square test for trend was used for the ordinal variables (DM score, adapted DM score and Blatteau score). The Mann-Whitney U test was used for scale variables since the values of these variables were not normally distributed (tested using Shapiro-Wilk test). Relative risk was calculated using the Mantel-Haenszel method. All tests were performed two-sided and statistical significance was accepted at $p < 0.05$.

RESULTS

A total number of 140 patients was treated with HBO₂ in the investigated period. From this total, 85 were diving accidents that received their first HBO₂ session in our institute. 70 of these patients were treated with

U.S. Navy Treatment Table 6 as their first treatment. Of this group, 50 were treated within 72 hours after the accident, 35 of whom had neurological signs and/or symptoms on admission and thus met our inclusion criteria. The total patient group consisted of 21 patients who were treated between 1996 and 2001 and did not receive lidocaine and 14 patients who were treated between 2001 and 2011 and did receive lidocaine.

General parameters of the patients are displayed in Table 2; a specification of the individual patients can be found in Tables 3a and 3b. Groups were comparable with regard to gender, age, body mass index, dive depth, dive time, breathing gas, percentage repetitive dives, time until start of symptoms, time until HBO₂, clinical course until start of HBO₂ and percentage of DCS and CAGE. Significantly more patients in the control group made an unsafe dive (62% vs. 14%, $p = 0.007$).

With respect to initial injury severity (Table 4), both groups had comparable DM, adapted DM and Blatteau scores. The differences between groups in regard to percentage of patients with objective neurological signs on admission (38% in the control group, 64% in the lidocaine group) was not statistically significant ($p = 0.176$). The number of treatment sessions given was similar in both groups. Treatment reduced DM score from 2.0 ± 1.6 to 0.1 ± 0.5 in the control group and from 2.7 ± 1.7 to 1.4 ± 3.0 in the lidocaine group, differences between groups were not statistically significant.

Percentage of patients with objective neurological signs at the end of the last HBO₂ session was 5% in the control group and 14% in the lidocaine group. DM score, adapted DM score and percentage of patients with objective neurological signs were not significantly different between groups at the end of the last HBO₂ session. The relative risk for unwanted outcome (objective neurological signs) when receiving lidocaine, corrected for objective neurological signs before first therapy, was 1.8 (95% confidence interval 0.2-16).

DISCUSSION

In this small retrospective cohort study, we were not able to demonstrate a positive effect of intravenous lidocaine vs. no lidocaine on outcome in patients with neurological DCI.

The use of lidocaine in DCI has been the subject of study for decades. Since the first report of a positive effect of this substance in preventing neurological injury in CAGE-induced in cats [17], multiple animal

TABLE 2: General and diving parameters

		control (n=21)	lidocaine (n=14)	p-value
sex	male	81%	71%	0.685
	female	19%	29%	
age (y)		36 (9.2)	36 (6.8)	0.946
body mass index (kg/m ²)		24 (3.4)	24 (2.8)	0.752
maximum diving depth (m)		24 (12)	30 (15)	0.224
diving time (min)		40 (14)	35 (13)	0.252
breathing gas	air	76%	79%	0.113
	nitrox	24%	7%	
	trimix	0%	14%	
repetitive dive		43%	57%	0.500
unsafe dive		62%	14%	0.007*
time until start of symptoms (h)		3.7 (7.0)	6.5 (11)	0.906
time until HBO ₂ (h)		16 (12)	22 (17)	0.418
clinical course until HBO ₂	better	24%	21%	0.985
	stable	48%	50%	
	worse	29%	29%	
diagnosis	DCS	86%	79%	0.664
	CAGE	14%	21%	

Values between parentheses are standard deviations. Percentages may not add up to 100% due to rounding errors. * = $p < 0.05$. Nitrox = breathing gas containing oxygen and nitrogen, in which the oxygen content is larger than in air. Trimix = breathing gas containing oxygen, nitrogen and helium.

and human studies have been performed on this matter. Lidocaine is a sodium channel blocker, which accounts for several of its neuroprotective effects, as reviewed by Mitchell [18,19]. Briefly, lidocaine is an anesthetic drug that depresses neuronal metabolism when given intravenously, rendering the brain less vulnerable when it is deprived of oxygen and furthermore lowering intracranial pressure. Secondly, lidocaine stabilizes the neuronal membrane, protecting the cell against damage in the case of ischemia. In the third place, its antiarrhythmic effect attenuates the cardiac arrhythmias that often occur in DCI and contribute to adverse outcome. Furthermore, apart from the effects due to sodium channel blocking, lidocaine has anti-inflammatory properties [20], which attenuate the inflammatory response associated with the endothelial damage that can occur in DCI. Several animal studies on lidocaine in CAGE confirmed the positive results

of the first investigation, not only when lidocaine was given as pretreatment, but also when given after induction of CAGE [4,21-23]. Animal studies on lidocaine in DCS were less unequivocal, with one study showing a positive effect [3] and other studies being unable to demonstrate better outcome [9,24]. Human studies on lidocaine in DCI are very scarce and limited to a few case reports [25-28] and a small retrospective study, of which unfortunately only an abstract has been published [29]. The most interesting data, however, come from four human studies on the use of intravenous lidocaine in cardiac surgery. Patients undergoing heart surgery are known to be at risk for postoperative neurocognitive decline, especially in open chamber surgery, and cerebral air embolization has been suggested as an important contributing factor [30]. Therefore, cardiac surgery may have similarities to diving-related CAGE. The first two studies, published

TABLE 3a: Clinical characteristics and diagnosis/Control group

sex	age	symptoms and signs	diagnosis
m	30	pain r shoulder, weakness triceps r	DCS
m	35	malaise, pain r/l knee, hypesthesia r trunk	DCS
m	38	paresthesia and hypesthesia l leg	DCS
m	45	vertigo, nausea, nystagmus	DCS-v
m	37	exhaustion, paresthesia l arm	DCS
f	21	ataxia, hypesthesia r face/arm/leg, weakness r arm/leg	CAGE
f	33	paresthesia and hyperesthesia l arm/leg, hyperreflexia l arm	DCS
f	29	exhaustion, headache, nausea, paresthesia l arm/leg	DCS
m	47	dyspnea, hemoptoe, paresthesia l foot	CAGE
m	32	paresthesia hyperesthesia and weakness r leg	DCS
m	30	paresthesia r/l arm	DCS
m	35	exhaustion, paresthesia back / r/l arm	DCS
m	25	somnolence, ataxia, paresthesia r/l arm/leg, hypesthesia r arm/leg	DCS
m	48	paresthesia and hyperesthesia l leg	DCS
m	25	paresthesia r foot/arm	DCS
f	34	dyspnea, headache, exhaustion, paresthesia neck/shoulders/arms	CAGE
m	44	paresthesia r/l arm	DCS
m	49	vertigo, nausea, nystagmus	DCS-v
m	36	dyspnea, exhaustion, pain r/l arm/leg, dysbasia	DCS
m	27	exhaustion, headache, paresthesia face / r/l leg, weakness l arm	DCS
m	56	paresthesia l arm	DCS

Clinical characteristics and diagnosis of the 21 patients in the control group.

r = right. l = left. DCS = decompression sickness. DCS-v = vestibular decompression sickness.

CAGE = arterial gas embolism.

in 1999 and 2002, showed a positive effect of lidocaine on postoperative neurocognitive decline in patients undergoing open chamber surgery patients [5] and coronary artery bypass grafting with cardiopulmonary bypass [6]. The two other studies, both published in 2009, included mixed groups of patients undergoing open chamber surgery or coronary artery bypass grafting. These studies failed to demonstrate a positive effect [7,8]. In fact, in one of these studies total lidocaine dose was an independent predictor of cognitive decline. All in all, based on these animal and human studies, lidocaine can be regarded as an interesting substance in DCI, but a positive effect has of yet not been proven. The only human studies showing beneficial effects have been performed in cardiac surgical cases, which may have similarities with CAGE but certainly not with other forms of DCI.

For the current study we included all patients who received lidocaine for neurological DCI and compared

these patients to an historical cohort. The control group was too small to perform a matched analysis, but the two groups were nevertheless comparable in regard to most confounding factors. Significantly more patients in the control group had made a dive that did not comply with decompression tables and guidelines, and can therefore be said to have suffered an “explainable” injury. This was however not reflected in increased disease severity since none of the injury scores showed statistically significant differences between groups. There was a trend toward increased risk of unwanted outcome in the lidocaine group (relative risk 1.8), even after correction for the larger percentage of objective neurological signs before start of therapy in the lidocaine group, but the large confidence interval (0.2-16) precludes any definitive statements. We must therefore conclude that we observed neither a positive nor a negative effect of lidocaine in our study.

TABLE 3b: Clinical characteristics and diagnosis/Lidocaine group

sex	age	symptoms and signs	diagnosis
m	30	exhaustion, paresthesia r/l leg & l hand, weakness r/l leg	CAGE
f	41	dyspnea, ataxia, paresthesia and hypesthesia r/l arm/leg	DCS
m	37	paresthesia r/l arm	DCS
f	32	paresthesia r/l hand, weakness r hand, areflexia r biceps	DCS
m	33	paresthesia r/l leg, hypesthesia l leg	DCS
m	33	paresthesia and hypesthesia l hand	DCS
m	27	dyspnea, paresthesia l hand, weakness l arm/leg	DCS
m	31	paresthesia and hyperesthesia r/l leg, areflexia l achilles	DCS
m	51	abdominal pain, paresthesia and hypesthesia r/l leg	DCS
f	34	ataxia, paresthesia l face/arm/leg, temporary visual field loss	DCS
m	35	tetraplegia	CAGE
m	29	exhaustion, nausea, vertigo, ataxia, paresthesia r/l arm/leg	DCS
f	34	ataxia, paresthesia r/l hand/foot & r trunk, hypesthesia l arm/ trunk/leg, weakness l arm/leg	CAGE
m	42	pain r arm, paresthesia r arm, subjective weakness r arm	DCS

Clinical characteristics and diagnosis of the 14 patients in the lidocaine group.
r = right. l = left. DCS = decompression sickness. CAGE = arterial gas embolism.

Our study is, of course, limited by its small sample size. Nevertheless, in our opinion this patient population represents the daily practice of the dive physician who faces relatively small numbers of patients with heterogeneous presentations. The heterogeneity is reflected in our study by the varying time until start of symptoms and time until start of HBO₂ therapy (although we limited our study group to patients receiving HBO₂ within 72 after symptom onset). Furthermore, we included all diseases that were eligible for adjuvant treatment with lidocaine: spinal DCS, cerebral DCS, vestibular DCS (together termed neurological DCS); and CAGE. One might argue to analyze these categories separately in order to determine whether lidocaine would have a beneficial effect in any of these subgroups. The small size of our population, however, precluded any meaningful subgroup analysis. Furthermore, it is not always possible to reliably distinguish the various forms of neurological DCI, and a patient may suffer from various types at the same time.

Symptom severity in our patients was relatively low on average, with DM scores of 2.0 ± 1.6 and 2.7 ± 1.7 (maximum possible score 10) in the control and lidocaine groups, respectively. We cannot rule out the possibility that more severely affected patients

would have benefited from lidocaine, but in our study subgroup analysis was not possible due to the small sample size. Furthermore, HBO₂ therapy was very effective in our control patients, leaving little room for further improvement due to lidocaine. On the other hand, a positive effect of lidocaine could also have been detectable as a lower number of HBO₂ sessions needed in the lidocaine group, which was not the case.

Our study suffers from possible bias since the control and lidocaine patients were not treated in the same period. The control patients were seen from 1996 to 2001, and the lidocaine patients from 2001 to 2011. Although, except for the addition of lidocaine, we are not aware of any differences in treatment between groups, although we cannot exclude the effect of time as a confounding factor.

The lidocaine dose used in our patients was in line with the doses used in previous investigations and the advice given by the Undersea and Hyperbaric Medical Society [31]. Although we did not obtain plasma levels of lidocaine in our patients, similar infusion strategies used in other studies resulted in lidocaine levels within the desired range [5-8]. We infused lidocaine during eight hours, starting at the beginning of the HBO₂ treatment. The duration of lidocaine administration varies

TABLE 4: Treatment and injury severity before and after HBO₂

	BEFORE first HBO ₂ session			AFTER last HBO ₂ session		
	control (n=21)	lidocaine (n=14)	p-value	control (n=21)	lidocaine (n=14)	p-value
number of treatment tables	n/a	n/a	n/a	2.0 (1.0)	2.7 (2.3)	0.537
Dick and Massey score	2.0 (1.6)	2.7 (1.7)	0.221	0.1 (0.5)	1.4 (3.0)	0.074
adapted Dick and Massey score	4.2 (2.6)	4.1 (2.6)	0.914	0.5 (1.0)	1.4 (3.0)	0.177
Blatteau score	5.4 (2.8)	7.4 (5.2)	0.152	n/a	n/a	n/a
objective neurological signs	38%	64%	0.176	5%	14%	0.551

Values between parentheses are standard deviations.

between the four published human studies. Two studies used a 48-hour lidocaine infusion [5,8], one study used 12 hours [7] and one study administered lidocaine intraoperatively, without mentioning the exact duration of the infusion [6]. There are currently no data that support any specific duration of lidocaine infusion.

The question remains if there is any future for the use of lidocaine in the treatment of neurological DCI. Our study is presently the most comprehensive investigation available, since larger and/or prospective studies are lacking. Although our study was underpowered to draw definitive conclusions, we have demonstrated that despite data collection over a period of 15 years in a relatively large hyperbaric center, we were not able to demonstrate a positive effect of lidocaine on neurological outcome in DCI. This is mainly caused by the small number of patients and the heterogeneity of the patient population.

Current Undersea and Hyperbaric Medical Society best practice guidelines on DCS and AGE discourage the use of lidocaine in DCS and are impartial on its use in AGE, only giving advice on lidocaine dose for those cases in which the physician chooses to use it [31]. The data on which these recommendations are based, as summarized in the present article, are weak and a prospective study on lidocaine in dive accidents is still lacking. We believe the most rational strategies would be to either abandon the use of lidocaine in neurological DCI altogether, or to perform a prospective study. Given the low prevalence of neurological DCI, the heterogeneous population and the fact that DCS and CAGE should be studied separately, this would call for a large multicenter investigation.

The authors report that no conflict of interest exists with this submission. ■

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