Cerebral protection by lidocaine during cardiac operations: a follow-up RDBCT

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Background

Lidocaine is a class Ib antiarrhythmic and local anesthetic. *In vivo* and *in vitro* experiments spanning 3 decades have established lidocaine as a neuroprotective agent, and putative neuroprotective mechanisms have been identified. This body of research is summarized by Mitchell (2001)[1]. Largely on the basis of neuroprotection during *in vivo* arterial gas embolism, lidocaine has been used in the treatment of decompression illness in divers with anecdotal success.[2,3] However, the only relevant human experiments have been conducted in cardiac surgery where brain injury may be caused by exposure to emboli, global hypoperfusion, or inflammatory responses in the peri-operative period. Neurocognitive deficits are relatively common in these patients.[4] Since the injury is common and function can be measured before and after injury, this group is ‘ideal’ for testing neuroprotective strategies.[5]

Previous studies

Mitchell et al. (1999)[6] published a small RDBCT (n = 65) conducted among valve surgery patients chosen for their relevance to diving (the LV is opened and there is considerable exposure to gas emboli). Fewer patients receiving lidocaine (standard antiarrhythmic dose for 48 hours) exhibited post-operative neurocognitive deficits (NCDs) at 10 d and 6 w.

Wang et al. (2002):[7] a larger RDBCT (n = 118), infusion during surgery only in coronary artery bypass graft (CABG) patients, also showing less NCDs in those given lidocaine (10 d follow up).

Mathew et al. (2009):[8] another larger RDBCT (n = 277), 48 hr infusion in CABG patients which did not show benefit. This result was not known at the time the present study was initiated.

The present study aimed to repeat our original work[6] in a larger group of cardiac surgery patients (including CABG), using a 12 hour (rather than 48 hour) lidocaine infusion.

Methods

- Randomized, double blind, intention to treat design.
- Power calculation based on results of original study for outcomes at 10 and 25 weeks[6]
- 158 patients recruited and completed a pre-operative battery of 7 neurocognitive tests.
-12 hour infusion of lidocaine (standard antiarrhythmic dose) or placebo beginning at induction of anesthesia.
- Confluent practice in anesthesiology (not rigidly standardized). Protocol based cardio-pulmonary bypass.
- Neurocognitive tests repeated at 10 and 25 weeks post-op with use of parallel forms where possible.
- NCD in any test defined as a decline in performance from pre-op baseline by ≥ group pre-op standard deviation for that test.

Results

- Recruitment, patient allocations and losses to follow up are compared for the study groups in Figure 1 (Consort diagram).
-The study groups are compared with respect to demographic, clinical, and surgical variables in Tables 1 & 2,

Table 1. Comparison of Study Groups With Respect to Important Demographic and Clinical Variables

Preoperative Factor	Lidocaine Group (n = 81)	Placebo Group (n = 77)
Age, years	61.5 (9.6)	58.1 (11.4)
Weight, kg	82.9 (15.8)	83.2 (14.9)
Male	60 (74.1%)	63 (81.8%)
Diabetes mellitus	9 (11.7%)	12 (17.1%)
Hypertension	34 (44.2%)	26 (34.2%)
Carotid disease	3 (3.7%)	7 (9.2%)
Left ventricular failure	5 (6.5%)	6 (7.9%)
Peripheral vascular disease	2 (2.6%)	5 (6.6%)
Current smoker	3 (3.7%)	8 (7.8%)
Previous cardiac surgery	4 (4.9%)	8 (9.9%)
NART result	34.6 (9.8)	33.1 (11.3)

Data are presented as mean (SD) or number (%).

NART = National Adult Reading Test.

Table 2. Comparison of Study Groups With Respect to Important Surgical and Perioperative Variables

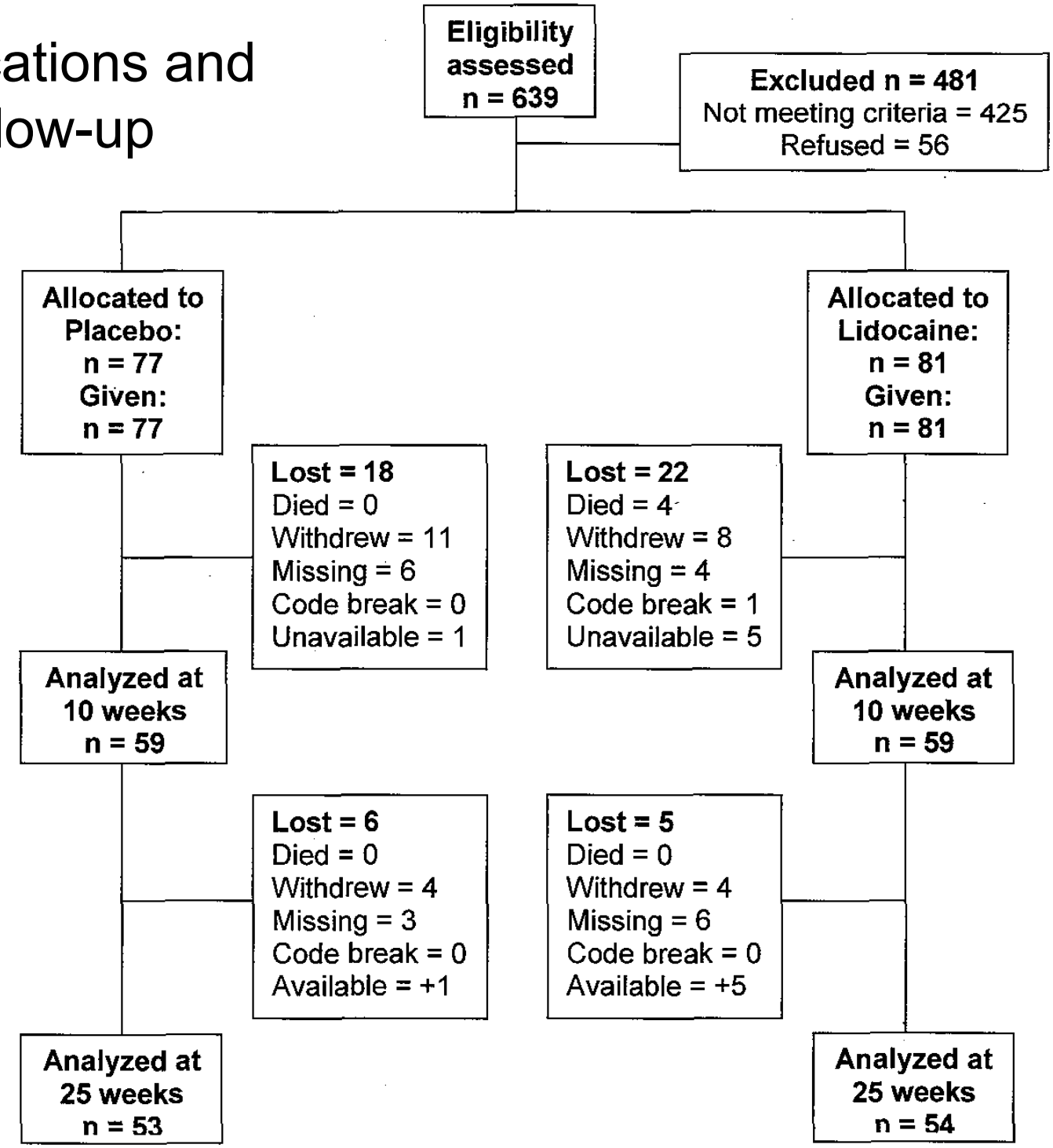
Perioperative Factor	Lidocaine Group (n = 81)	Placebo Group (n = 77)
AVR	3 (3.7%)	3 (3.9%)
MVR	5 (6.2%)	1 (1.3%)
AVR plus MVR	1 (1.2%)	0
CABG on pump	58 (71.6%)	54 (70.0%)
OPCABG	10 (12.3%)	8 (10.4%)
Valve plus CABG	4 (4.9%)	11 (14.3%)
Bypass time, minutes	109.4 (34.3)	110.6 (42.1)
Minimum temperature, C	32.4 (1.8)	32.2 (1.7)
Inotropes after CPB	47 (58.0%)	40 (51.9%)
Total emboli exposure[a]	124.5 (2–3,263)	160.49 (5–3,484)

[a] Data are geometric mean (range).

Data are shown as mean (SD) or number (%), unless otherwise specified.

AVR = aortic valve replacement; CABG = coronary artery bypass graft surgery; MVR = mitral valve replacement; OPCABG = off-pump CABG.

Figure 1.
Patient allocations and losses to follow-up



Results

- The study groups are compared with respect to NCDs at 10 and 25 week follow ups in Table 3.

Table 3. Comparison of Study Groups With Respect to Proportion of Patients Exhibiting a Neurocognitive Deficit at Each Follow-Up

10-Week Lidocaine (n = 59)	Placebo (n = 59)	*p* Value	25-Week Lidocaine (n = 54)	Placebo (n = 53)	*p* Value
27 (45.8%)	24 (40.7%)	0.577	19 (35.2%)	20 (37.7%)	0.710

Discussion

- Lidocaine was not neuroprotective
- The result of original study may have been a Type 1 error, however, the present study involved mainly CABG patients who are exposed to less emboli than the open chamber patients enrolled in the first study. It is possible that lidocaine is most protective when the injury is mainly (air) embolic.
- This result, together with that of the Duke study[8] makes the role of lidocaine in treatment of arterial gas embolism (AGE) and decompression sickness even less certain. However, since the mechanism of injury in AGE is different to that suffered by the majority of patients developing NCDs in this study, a potential for benefit in AGE should not be excluded on the basis of these results.
- This study was published in March this year.[9]

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