

Table of contents

ACKNOWLEDGEMENTS.....	i
TABLE OF CONTENTS.....	iv
LIST OF TABLES.....	xi
LIST OF FIGURES.....	xiv
ABBREVIATIONS.....	xvii
ABSTRACT	i
CHAPTER 01	xxiii
Introduction	xxiii
1.1 Epidemiology	xxiv
1.2 Management of OP/PQpoisoning.....	xxx
1.3 Antioxidant therapy in paraquat poisoning	xxxi
1.4 Evidence of neurotoxicity from previous studies	xxxiv
1.5 Rationale, aims and objectives of the present study	xxxvi
CHAPTER 02	xxxviii
Materials and methods	xxxviii
2.1 Study design	xxxix
2.2 Ethical considerations.....	xl
2.3 Calculation of sample size.....	xl
2.4 Participants	44
2.5 Informed consent	46
2.6 Data collection.....	47
2.7 Clinical investigations	47
2.8 Bio-chemical investigations	51
2.9 Electrophysiological Investigations.....	62

2.10 Assessment of cognitive function.....	64
2.11 Screening test of psychiatric illness - General Health Questionnaire	65
2.12 Ultrasonographical investigation.....	66
2.13 National guidelines on the management of OP poisoning	67
2.14 National guidelines on the management of paraquat poisoning.....	68
2.15 Statistical analysis	69
CHAPTER 03	70
Effects of acute organophosphorus poisoning on function of peripheral nerves	70
3.1 Introduction	71
3.2 Materials and methods.....	71
3.3 Results	77
3.4 Discussion.....	80
3.5 Limitations.....	84
3.6 Conclusions	85
CHAPTER 04	86
Autonomic dysfunction following acute organophosphorus poisoning.....	86
4.1 Introduction	87
4.2 Materials and methods.....	87
4.3 Results	93
4.4 Discussion.....	103
4.5 Limitations.....	106
4.6 Conclusion	106
CHAPTER 05	107
Function of the neuromuscular junction in patients with acute organophosphorus poisoning after the clinical recovery.....	107

5.1 Introduction	108
5.2 Materials and methods.....	109
5.3 Results	112
5.4 Discussion.....	116
5.5 Conclusion.....	118
CHAPTER 06	119
Subclinical peripheral nerve, autonomic nerve and neuro-muscular junction dysfunction following self poisoning with paraquat	119
6.1 Introduction	120
6.2 Materials and methods.....	122
6.3 Results	135
6.4 Discussion.....	149
6.5 Conclusions	153
CHAPTER 07	154
Effects of deliberate ingestion of organophosphate or paraquat on brain stem auditory evoked potentials	154
7.1 Introduction	155
7.2 Materials and methods.....	155
7.3 Results	156
7.4 Discussion.....	160
7.5 Conclusion.....	163
CHAPTER 08	164
Effects of acute organophosphate or paraquat ingestion on cognitive function; assessed with the Mini Mental State Examination.....	164
8.1 Introduction	165
8.2 Materials and methods.....	165

8.3 Results	169
8.4 Discussion.....	172
8.5 Conclusions	176
8.6 Limitations.....	176
CHAPTER 09	177
Psychological distress among patients with organophosphorus or paraquat poisoning	
.....	177
9.1 Introduction	178
9.2 Materials and methods.....	178
9.3 Results	180
9.4 Discussion.....	181
9.5 Conclusion.....	184
9.6 Limitations.....	184
CHAPTER 10	185
Adherence to the National Guidelines on the Management of Organophosphorus Poisoning	
.....	185
10.1 Introduction	186
10.2 Materials and methods.....	187
10.3 Results	187
10.4 Discussion.....	194
10.5 Conclusion.....	195
CHAPTER 11	196
Adherence to current guidelines for the management of paraquat poisoning	196
11.1 Introduction	197
11.2 Materials and methods.....	197
11.3 Results	198

11.4 Discussion.....	201
11.5 Conclusion.....	202
CHAPTER 12	203
Effects of intravenous vitamin C and N-acetylcysteine in acute paraquat poisoning: randomized double blind placebo controlled trial	203
12.1 Introduction	204
12.2 Methods	206
12.3 Results	210
12.4 Discussion.....	222
12.5 Conclusion.....	223
CHAPTER 13	224
Effects on peripheral nerve, autonomic and neuromuscular junction function with antioxidant therapy in acute paraquat poisoning	224
13.1 Introduction	225
13.2 Materials and methods.....	226
13.3 Results	232
13.4 Discussion.....	232
13.5 Conclusion	237
CHAPTER 14	238
Possibility of direct toxic effects on the central nervous system following acute paraquat poisoning.....	238
14.1 Introduction	239
14.2 Materials and methods.....	239
14.3 Results	240
14.4 Discussion.....	240
14.5 Conclusion	242

CHAPTER 15	243
Discussion.....	243
15.1 Neurotoxic effects of organophosphorus.....	244
15.2 Neurotoxic effects of paraquat	253
15.3 Cognitive function of OP or PQ poisoned patients	257
15.3 Psychological status of OP or PQ poisoned patients.....	258
15.4 Antioxidant trial.....	260
15.5 The paraquat concentration in post-mortem cerebrospinal fluid to determine the extent of the diffusion across the blood brain barrier.....	262
15.6 The adherence to existing guidelines on the management of OP or paraquat poisoning	263
CHAPTER 16	266
Conclusions	266
References	269
Appendix – 1	283
Letter of ethical clearance.....	283
Appendix – 2	285
Registration in Sri Lanka Clinical Trial Registry.....	285
Appendix – 3	286
Information sheets and consent forms	286
Appendix – 4	301
General Health Questionnaire (GHQ)	301
Appendix – 5	303
Mini Mental State Examination (MMSE)	303
Appendix – 6	307
Data record sheets.....	307

Appendix – 7	319
Assay details of glycated hemoglobin (HbA _{1C})	319



List of tables

Table 2.1	Mean \pm SD of parameters and calculation of sample size for the organophosphorus neurotoxic trial.....	22
Table 2.2	Mean \pm SD of parameters and calculation of power for the paraquat neurotoxic trial.....	23
Table 2.3	The Medical Research Council scale for grading muscle function.....	30
Table 2.4	Tests of cardiovascular autonomic function.....	44
Table 2.5	Cut-off values of cardiac autonomic function tests.....	45
Table 2.6	Settings for electrophysiological assessment.....	62
Table 3.1	Descriptive data of the patients and the controls.....	79
Table 3.2	Number of poisoned cases by type of OP.....	79
Table 3.3	Effects of acute OP on peripheral nerve function.....	81
Table 3.4	Studies of pesticide exposure and peripheral nerve function.....	83
Table 4.1	Cut-off values of autonomic function tests.....	90
Table 4.2	Descriptive data of the participants.....	96
Table 4.3	Number of poisoned cases by type of OP.....	97
Table 4.4	Autonomic function assessment in patients and controls.....	99
Table 4.5	Results of the blood pressure response to sustained hand grip.....	100
Table 4.6	Step wise multiple linear regression analysis for autonomic function tests.....	101
Table 5.1	Descriptive data of the test and the control group.....	113
Table 5.2	Decrement response, post exercise facilitation and post exercise	114

	exhaustion of the patients and the controls.....	
Table 5.3	The number of participants who showed more than 8% decrement when considering the second, fourth or fifth stimuli.....	115
Table 6.1	Cut-off values of autonomic function tests based on cardiovascular reflexes.....	130
Table 6.2	Peripheral nerve conduction studies in the patients and the controls.....	137
Table 6.3	Autonomic function of the patients and the controls.....	139
Table 6.4	The test of blood pressure response to sustained hand grip.....	141
Table 6.5	The comparison of neuromuscular junction function in the first assessment of the test group and the controls.....	143
Table 6.6	The comparison of the first and the second assessment of the test group.	144
Table 6.7	Correlation of nerve conduction studies with markers of oxidative stress and plasma PQ concentration.....	145
Table 6.8	Correlation of autonomic nerve function with markers of oxidative stress and plasma PQ concentration.....	147
Table 6.9	Correlation of NMJ function with markers of oxidative stress and plasma PQ concentration.....	148
Table 7.1	The mean latency difference of BAEP in the test and the control groups in OP poisoning.....	161
Table 7.2	The mean latency difference of BAEP in the test and the control groups in PQ poisoning.....	162
Table 8.1	Comparison of the Sinhalese translation of the MMSE with the MMSE administered in our study.....	167
Table 8.2	Questionnaire used to assess long term memory.....	168
Table 8.3	Distribution of gender and level of education in the patients and the	170

controls.....		
Table 8.4	Mean (SD) score of individual domains in the MMSE.....	171
Table 8.5	The mean (SD) of digit span test, long term memory function and concentration.....	173
Table 8.6	Cognitive function of PQ patients.....	174
Table 9.1	Descriptive data of the participants.....	179
Table 9.2	Adjusted multiple linear regression for confounders.....	182
Table 10.1	Outcome following hospital admission.....	188
Table 10.2	Receiving of loading and maintenance doses of pralidoxime.....	193
Table 11.1	Details of the patients who did not receive Fuller's earth.....	199
Table 11.2	Regimens of immunosuppression therapy in the collaborating hospitals..	200
Table 12.1	Descriptive data of three groups.....	212
Table 12.2	Comparison of vitamin C + placebo Vs vitamin C + NAC arms.....	215
Table 12.3	Multiple Linear Mixed Model for antioxidant levels.....	219
Table 13.1	Comparison of peripheral nerve function of the test individuals with controls.....	234
Table 13.2	Comparison of autonomic function of the test individuals with the controls.....	235
Table 13.3	Comparison of NMJ the test individuals with the controls.....	236
Table 14.1	Plasma and CSF paraquat levels.....	241
Table 14.2	Correlation matrix of pre and post mortem plasma paraquat and CSF paraquat levels.....	241

List of figures

Figure 2.1	Pupil scale.....	30
Figure 2.2	Formation of HbA _{1C}	31
Figure 2.3	Principle of the procedure of estimation of Hb A _{1C} by HPLC.....	34
Figure 2.4	Semi-quantitative assessment of urine paraquat level by sodium dithionite test.....	35
Figure 2.5	Paraquat test kit.....	35
Figure 2.6	Chemical reactions in sodium dithionite with paraquat.....	35
Figure 2.7	Assay procedure of Human Clara Cell Protein ELISA.....	40
Figure 2.8	Assay procedure of Human Surfactant Protein D (SP-D) ELISA.....	41
Figure 2.9	EMG/EP measuring system.....	44
Figure 2.10	Placement of ECG electrode attachments for the assessment of R-R interval variability.....	46
Figure 2.11	Hand dynamometer.....	48
Figure 2.12	Position of the individual when measuring the blood pressure response to sustained hand grip.....	48
Figure 2.13	Electrode placement and stimulation site in SSR.....	51
Figure 2.14	Rectified and superimposed SSR complexes.....	51
Figure 2.15	Electrode placement in BERA.....	61
Figure 3.1	Sensory nerve action potential.....	74
Figure 3.2	Motor nerve compound muscle action potential.....	75
Figure 3.3	Occurrence and latency of F-waves.....	76

Figure 3.4	Flow diagram of recruitment of participants.....	77
Figure 4.1	ECG electrode attachments for the assessment of R-R interval based autonomic function tests.....	90
Figure 4.2A	Normal SSR.....	92
Figure 4.2B	Absent response to SSR.....	92
Figure 4.3	Recruitment of the participants to the study.....	95
Figure 5.1A	Normal response to slow repetitive supramaximal stimulation.....	111
Figure 5.1B	Decrement response to slow repetitive supramaximal stimulation.....	111
Figure 6.1	Sensory nerve action potential.....	125
Figure 6.2	Motor nerve compound muscle action potential.....	126
Figure 6.3	Occurrence and latency of F-waves.....	127
Figure 6.4A	Normal SSR.....	132
Figure 6.4B	Absent response to SSR.....	132
Figure 6.5A	Normal response to slow repetitive supramaximal stimulation.....	134
Figure 6.5B	Decrement response to slow repetitive supramaximal stimulation.....	134
Figure 7.1	Electrode placements in BAEP.....	157
Figure 7.2	Interpeak latencies of BAEP.....	158
Figure 7.3	Probable sites of generation of the human BAEP.....	159
Figure 10.1	Prevalence of cholinergic features.....	190
Figure 10.2	Features of atropine toxicity.....	191
Figure 10.3	Adequacy of atropine therapy.....	192

Figure 12.1	Recruitment of the test individuals for the study.....	208
Figure 12.2	Survival functions of the tests and the controls.....	213
Figure 12.3	Survival function according to the gender in the test group vs historical controls.....	216
Figure 12.4	Survival function according to the gender in the test group vs parallel controls.....	217
Figure 12.5	Plasma antioxidant levels in tests and historical controls	220
Figure 12.6	Survival statuses according to the plasma paraquat concentration.....	221