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Review

Can we predict intermediate syndrome? A review

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ABSTRACT

Introduction: Ingestion of organophosphorus insecticides (OPI) is a common method of deliberate self harm in the developing world. Deaths mainly follow as a result of the respiratory failure associated with both cholinergic crisis and the intermediate syndrome. Even though death can be prevented by early mechanical ventilation of these patients, limited studies are available regarding the prediction of intermediate syndrome and subsequent respiratory failure.
Objective: To systematically review articles that are published with regard to possible prediction of intermediate syndrome using clinical, biochemical and electrophysiological parameters.
Methods: A systematic review on literature published in English language was done in the PubMed database without a date limitation. Two sets of search terms were used. The first set consisted of MeSH Terms “organophosphates”, “organophosphate poisoning”, “op poisoning” “organophosphate insecticide poisoning” and “organophosphorus”. The second set included the MeSH Terms “Intermediate syndrome”, “proximal muscle weakness”, “cranial nerve palsies”, “respiratory depression” and “neck muscle weakness”. Articles containing at least one word from each set were reviewed.
Results: At least one MeSH term from each set was incorporated in 179 articles. Of these, 69 were rejected as they were not related to organophosphate poisoning or intermediate syndrome.
Prediction of IMS: Clinical prediction is mostly based on ICU scoring systems. Biochemical markers such as reduced levels of serum and erythrocyte acetylcholine esterase have been studied many times. Both clinical and biochemical markers show a modest relationship in predicting IMS. Single fibre electromyography show promising results as it directly assesses neuromuscular junction.
Conclusion: The intermediate syndrome which follows organophosphate poisoning still remains a significant problem with its high morbidity. Clinical and biochemical markers show modest results in predicting IMS. Neurophysiological markers such as single fibre EMG should be studied further as they measure activity of affected nicotinic receptors directly.

Contents

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1. Introduction

Ingestion of organophosphorus insecticides (OPI) is a common method of suicide in the world (Yanga and Deng, 2007; Eddleston et al., 2006a).There are about 13 types of OPI which are derivatives of phosphoric or phosphonic acid. All OPI have one thing in common: a phosphorus atom and a characteristic phosphoryl bond (Gupta, 2006). Currently WHO hazard class II compounds are more in use following the bans on highly toxic compounds in class I (Manuweera et al., 2008; Peter et al., 2010).The reasons behind these poisonings are multifactorial (Eddleston et al., 2006a, 2006c, 2005; van der Hoek and Konradsen, 2005; Manuel et al., 2008; Eddleston, 2000). Despite methods to ban certain highly toxic pesticides, hospital admissions and the case fatality ratio still remains high highlighting the disease burden to countries like Sri Lanka (Rajapakse et al., 2014; Eddleston et al., 2006b; Wickramasinghe et al., 2009). Usually the deaths are a result of respiratory failure associated with the poisoning. Respiratory failure following OPI poisoning is either due to the initial cholinergic crisis or the intermediate syndrome (IMS) (Eddleston et al., 2005; Lotti and Moretto, 2005; Senanayake and Karalliedde, 1987; Sedgwick and Senanayake, 1997; KD, 2017). The OPI binds with the acetylcholine esterase (AchE) enzyme which is responsible for degrading acetylcholine in the synaptic cleft, leading to accumulation of acetylcholine and subsequent blockage of the neuromuscular junction. However with aging of the enzyme, this binding becomes irreversible (Jayawardane et al., 2008; King and Aaron, 2015; Andrew and King, 2015). Carbamate compounds have a similar action though the impact is less due to their reversible nature of the binding without aging (Andrew and King, 2015). Despite banning of highly toxic OPI compounds, IMS persists to be a problem requiring a significant amount of health care facilities causing a significant burden to the countries affected.

2. Intermediate syndrome

With the current understanding, the clinical sequence of poisoning with OPI can be categorized mainly into three phases; the acute cholinergic crisis, the intermediate syndrome (IMS) and delayed polyneuropathy. Classically, the onset of IMS is between 24 and 96 h following ingestion once the acute cholinergic features have waned off (Senanayake and Karalliedde, 1987). A prospective definition was taken into account in a paper published in 2008 where if three muscles of extraocular, neck flexor, proximal limb or facial muscles were paralysed the patient was considered to be having IMS (Jayawardane et al., 2008).

The incidence of IMS varies from 17 to 80% (Yanga and Deng, 2007; Jayawardane et al., 2008; Kim et al., 2013; Indira et al., 2013). IMS is usually seen in patients who had ingested a highly toxic OPI with high lipid solubility, higher dose ingestion or a late presentation to the hospital (Eddleston et al., 2012; De Bleecker et al., 1993). IMS is characterized by weakness of the limb girdle and proximal limb muscles and the neck flexors, cranial nerve palsies, and subsequent respiratory failure due to paralysis of the diaphragm, intercostal muscles and other accessory respiratory muscles (Senanayake and Karalliedde, 1987; Jayawardane et al., 2008). A more comprehensive explanation of the neuromuscular junctional blocking was forwarded in 1997 based on down regulation of acetylcholine receptors (Sedgwick and Senanayake, 1997).

Apart from this neuromuscular junctional impairment has also been attributed to the presence of persistent AchE inhibition, muscle fibre necrosis, desensitization of post synaptic acetylcholine receptors, failure of post synaptic acetylcholine release or oxidative stress related myopathy (Eddleston et al., 2012; Abdollahi and Karami-Mohajeri, 2012; Gaspari and Paydarfar, 2007, 2009; van Helden et al., 1991; Karalliedde et al., 2006; Karalliedde and Henry, 1993).

As IMS remains a major contributor to deaths associated with respiratory failure, susceptible patients need close observation and monitoring (Hulse et al., 2014). In an experiment conducted in rats with high dose organophosphorus poisoning, the researchers propose a two hit model, where initial respiratory depression due to central apnoea associated with cholinergic crisis is followed by progressive pulmonary insufficiency with excessive secretions leading to a subsequent respiratory depression (Gaspari and Paydarfar, 2007). However, in clinical studies, no clear cut demarcation has been observed between the initial respiratory depression associated with the cholinergic crisis and the respiratory depression associated with IMS further stressing the need for close observation (Eddleston et al., 2006d).

Despite banning of highly toxic compounds, the incidence of IMS and related deaths continues to persist (Lamb et al., 2016). Most of these IMS patients require prolonged ventilatory support in intensive care units (ICU) and require to be transferred to tertiary care hospitals for further management in ICUs (Jayawardane et al., 2008, 2012; Hulse et al., 2014). As IMS contributes to a significant morbidity and mortality, early prediction of IMS is vital (Rosenbaum and Bird, 2010). Whether there are clinical, biochemical or neurophysiological markers that can predict the onset of the disease still remains a major question (Jayawardane et al., 2012; Aygun et al., 2002, 2007; Brahmi et al., 2006; Colak et al., 2014; De Bleecker et al., 1992a). Therefore we conducted a literature review to find out about the availability of possible predictors of IMS in clinical populations.

2.1. Methodology

A systematic review on literature published in English was conducted in PubMed database without a date limitation. Both human and animal studies were included. Two sets of search terms were used. The first set consisted of Medical Subject Heading (MeSH) terms (“organophosphates”, “organophosphate poisoning”, “OP poisoning” “organophosphate insecticide poisoning” and “organophophorus”. The second set included the MeSH Terms “Intermediate syndrome”, “proximal muscle weakness”, “cranial nerve palsies”, “respiratory depression” and “neck muscle weakness”.

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3. Results

At least one MeSH term from each set was incorporated in 179 articles. Of these, 69 were rejected as they were not related to organophosphate poisoning or intermediate syndrome. Articles containing at least one word from each set were reviewed.

Of the 110 articles, 3 articles related to clinical prediction of IMS, 7 articles related to biochemical prediction of IMS and 6 articles related to electrophysiological prediction of IMS were reviewed (Fig. 1).

4. Results

There were three articles related to clinical prediction of IMS or respiratory failure and mortality (1 prospective study and 2 retrospective studies). The prospective study aimed at the prediction of IMS, and the two retrospective studies mainly focused on prediction of respiratory failure and mortality.

We retrieved seven publications on biochemical prediction of IMS or respiratory failure associated with OPI poisoning (5 prospective cohort studies and 2 retrospective cohort studies). Of those, three studies discussed prediction of IMS while the others focused on respiratory failure and hospitalization.

Electrophysiological prediction and related articles comprised 3 case reports, 2 case series and one prospective cohort study.

4.1. Prediction based on clinical parameters and scoring systems

Clinical studies available are related to prediction of respiratory failure rather than IMS and they mainly focus on different scoring systems which are used in ICUs to assess the clinical status of the patient. These involve alteration of physiological and biochemical parameters. Two of these studies are retrospective studies which were based on old hospital records and they do not state the exact time of appearance of clinical symptoms or measurement of enzyme levels from the time of the ingestion of the OPI compound. Of the two retrospective studies one study focused on predicting mortality in OPI ingested patients using clinical scoring systems and therefore was excluded (Ratanarat et al., 2005). A prospective cohort study conducted in a tertiary care hospital in India, had evaluated 176 patients presented within 24 h following OP poisoning using the International Program on Chemical Safety Poison Severity Score (IPCS PSS) a standardized scale for grading the severity of poisoning for qualitative evaluation of morbidity associated with poisoning, and Glasgow Coma Scale (GCS). Receiver operating characteristic (ROC) curves were drawn for the occurrence of IMS against the scores obtained. Of the 50 patients diagnosed with IMS, neck muscle weakness (mean time 44.5 ± 22.1 h after exposure) was the initial symptom seen. Neck muscle power was considered to be weak if the patient was unable to move the neck against gravity (Medical Research Council grade 3). 20/26 patients had respiratory failure between 0 and 8 h after the onset of the muscle weakness (mean 3.1 ± 2.5 h). Mortality was 28.4% in the full cohort and 40% in the IMS group. For IPCS PSS >2, the area under the curve (AUC), sensitivity, and specificity were 0.77, 0.94 and 0.6 respectively. For GCS <10, the area under the curve, sensitivity and specificity were 0.64, 0.71, 0.65. The conclusions were that the risk of IMS maybe high with age >45 years, with initial IPCS PSS score >2, GCS <10 and early detection is better with detecting neck power weakness (Indira et al., 2013). The main weakness of this study is that exposure was not confirmed by plasma OPI levels or acetylcholine esterase (AChE) levels. Even though the study mentions of 31 patients with IMS, data involves only 26 patients. Further,the time of appearance of

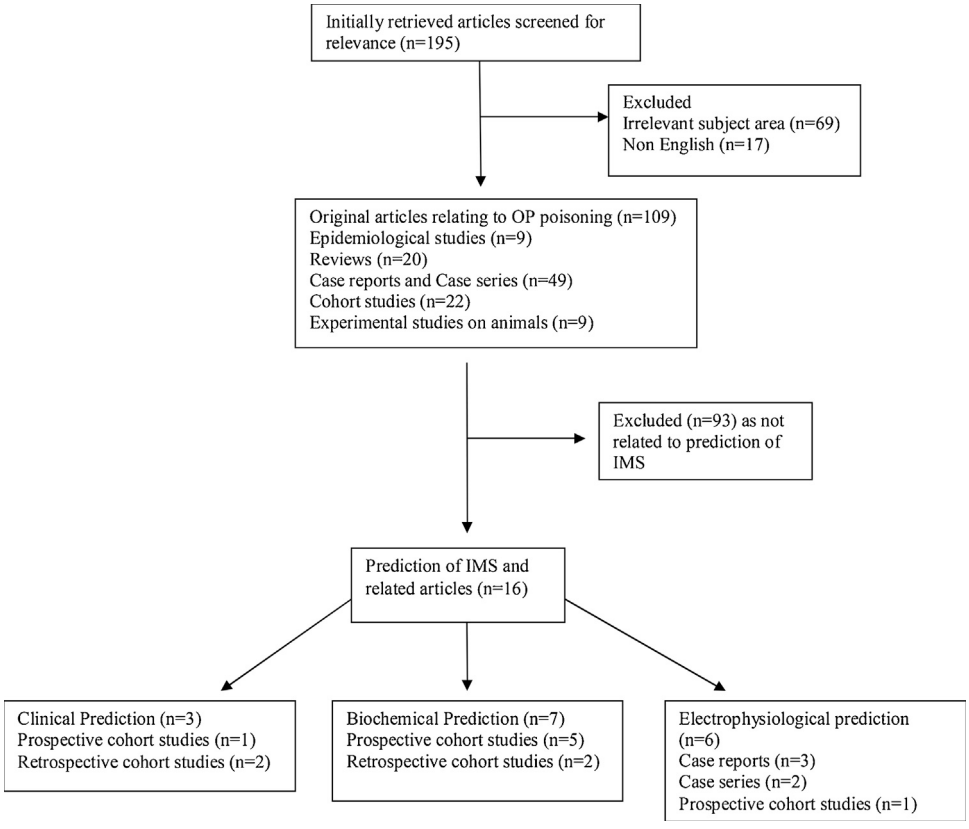

Fig. 1. Selection process of studies.

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clinical symptoms such as neck muscle weakness following ingestion of the compound was not specified.

A retrospective cohort study conducted using 396 patients compared Acute Physiology and Chronic Health Evaluation II score (APACHE II), Simplified Acute Physiology Score (SAPS) and Poisoning Severity Score (PSS) (Peter et al., 2013). In the ROC curves drawn for each scoring system, the AUC for APACHE II, SAPS II, and PSS were 0.77, 0.77 and 0.67 respectively indicating the prediction of respiratory failure (65.7%) and mortality (13.1%) was better with APACHE II and SAPS II scoring systems compared to PSS. The AUC for APACHE II score was highest for quinalphos and chlorpyrifos (WHO class II compounds) indicating the high human toxicity of these compounds (Peter et al., 2013). The AUC for all scores in patients poisoned with monocrotophos and methyl parathion were much lower indicating their low toxicity. There was a patient selection bias as only ICU patients were recruited and all the data were extracted from old records retrospectively. The confirmation of ingestion was based on history, clinical features and low levels of butyrylcholinesterase (BchE). A significant number of patients were included in the study without identification of the OPI compound, provided the patients had cholinergic features (n = 145).In medical ICUs general prediction of morbidity and mortality in all patients was found to be better with APACHE II scoring system than SAPS indicating the better use of APACHE II score in predicting the possibility of IMS as the AUC in each graph was higher in these two scoring systems (AUC 0.7-0.8 i.e. acceptable/fair prediction) than the ROC curve drawn for PSS (AUC 0.6-0.7, i.e. poor predictive ability) (Ratanarat et al., 2005). The study mainly focuses on predicting the mortality rather than IMS in acute OPI poisoning (Kim et al., 2013).

Overall, the predictive ability of ICU scoring systems like IPCS PSS and APACHE II can be used to predict the occurrence of IMS.

4.2. Prediction based on biochemical parameters

Literature on biochemical parameters related to prediction of possible OPI poisoning and its severity include measurement of serum choline esterase (SChE), erythrocyte membrane acetylcholine esterase levels (EAchE), serum creatinine kinase (CK) levels, and serum amylase levels. Even though the extent of the toxicity in poisoning cannot be accurately assessed by measuring these enzyme levels, it is an acceptable surrogate marker of OPI exposure (Worek et al., 2005; Patel et al., 2012).

A study done in 2006 by Brahmi et al. using 42 patients with OPI ingestion revealed that there is a significant difference of EAchE levels between comatose and non-comatose patients. Also ROC curves drawn for EAchE against hypotension, mechanical ventilation and bradycardia had AUC of 0.75, 0.75 and 0.73 respectively, making EAchE a possible marker to predict respiratory failure and impending haemodynamic instability (Brahmi et al., 2006). However in this study, the authors did not differentiate cholinergic respiratory failure from IMS.

A retrospective cohort study done in 2014 revealed that, 11 out of 71 patients developed IMS, but the specific time of diagnosis is unclear, i.e. “between the cholinergic crisis and the delayed polyneuropathy”. The diagnosis was made based on the weakness of proximal limb muscles, neck flexors, respiratory muscles and motor cranial nerves, but the severity of the symptoms were not mentioned. Low SChE levels ($p < 0.01$), and high blood glucose levels ($p = 0.037$) were seen which may be useful in predicting the occurrence of IMS (Colak et al., 2014). There is a patient selection bias as the researchers had only checked available ICU medical records. The subjects were not assessed by the researchers. Also ROC curves were not drawn with AUC, sensitivity and specificity to convey the predictive ability of these two tests.

A study done by Dandapani et al. in 2003, had tested blood samples of 19 severely OPI poisoned patients for E.AchE levels and serum butyrylcholinesterase levels (BchE) daily, with markers of possible oxidative stress (Dandapani et al., 2003). Sixteen of 19 patients developed IMS. Both EAchE and BchE levels were reduced since admission and throughout the course of the disease compared to healthy controls ($p < 0.001$). But there was no significant difference between patients with IMS and patients without IMS making these findings obsolete in diagnosing impending IMS. Significant higher levels of lipid peroxidation, conjugated dienes and protein thiols on red cell membranes of IMS patients were present compared to the controls ($p < 0.05$). They have compared IMS patients and control patients based on their temporal profiles of lipid peroxidation and conjugated dienes in erythrocyte membranes using ROC curves which they found to be significant. Based on this the authors concluded that prolong inhibition of EAchE levels were associated with increased oxidative stress to the red cells which could reflect a similar damage to muscles, which may play a role in development of IMS (Dandapani et al., 2003). Patients were recruited based on history, clinical features and low butyrylcholine esterase (BchE) levels.Assuming that the oxidative damage to red cells may reflect a similar change in muscles is a problem in the study where muscle damage could have been assessed directly.

Another study done by Aygun et al. in 2007 reported that low SChE levels recorded (if the lowest SChE level was <50% less than the lab minimum normal value) within the first 24 h has no predictive ability of IMS (Aygun et al., 2002). Student’s *t* test has been used to compare SChE levels between patients with mild and severe poisoning and therefore these results do not have a predictive ability.

A study conducted by the same team in 2007 tested the possible association between serum creatinine kinase (SCK); an enzyme released in muscle damage, and the occurrence of IMS. 47 patients were assessed of whom 10 patients developed subsequent IMS. The conclusion was that the muscle enzyme levels measured within the first 24 h (SCK and aspartate aminotransferase) cannot predict the occurrence of IMS as there was no significant difference in the initial enzyme levels between IMS patients and others with mild poisoning (Aygun et al., 2007). In this study patient records were assessed retrospectively, with a selection bias in the cohort. Method of diagnosis of OPI poisoning is not stated clearly.

Another study was on the usefulness of serum amylase enzyme (SAE) levels in predicting IMS by Lin et al. in 2004. This study was conducted in 42 patients. On admission the patients were subjected to the measurement of SAE and plasma acetylcholinesterase levels (PAchE). Plasma amylase level on the group who developed respiratory failure in the emergency ward was significantly higher compared to the group who did not develop respiratory failure ($p < 0.01$). But the study does not specify whether respiratory failure was associated with cholinergic crisis or IMS. The researchers also found that bradycardia, hypotension, muscle fasciculation and coma were significantly associated with respiratory failure. Their conclusion was that plasma amylase levels were a positive predictor of impending respiratory failure (Lin et al., 2004). However they do not comment on the time of respiratory failure which could be associated either with cholinergic crisis or IMS. Also these conclusions were based on student’s *t*-test p values which do not have any predictive ability.

A Chinese study in 2008 reveals the importance of acid base imbalance associated with morbidity and mortality following OPI poisoning. Retrospective data of 82 OPI poisoned patients were studied within the first 24 h of admission. With the initial blood gas analysis patients were grouped into those without acidosis, with metabolic acidosis, with respiratory acidosis and those with mixed acidosis. Of the metabolic acidosis group 25% of the patients died

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Table 1
Summary of the studies reviewed in relation to possible prediction of IMS.

Author	Year of Publication	Type of Study	Number of Patients	Confirmation of OPP	Acknowledment of ingestion time	Enzyme assays/blood Ix done	Conclusion	Limitations
	Clinical							
Indira M	2013	Prospective observational cohort study	176 IMS: 31		Yes		Higher risk of IMS with age >/=45 years, admission score PSS >2, GCS </=10 Earliest sign of IMS is neck muscle weakness.	There was no confirmation of the poisoning by organophosphates. Serum AchE levels were not done. Extent of the neck muscle weakness is not specified. No specification on prediction of IMS.
Peter J V	2013	Retrospective cohort study	396		No	Pseudocholine esterase levels	In acute OP poisoning APACHE II and SAPS II outperform PSS in predicting mortality.	Patient selection bias. Main focus is on predicting mortality rather than IMS.
	Biochemical							
Brahmi N	2006	Prospective cohort study	42		No	Erythrocyte acetylcholine-esteraselevels	Reduced levels of EAchE has a prognostic value in predicting coma, respiratory failure, haemodynamic disturbances and death in acute OP poisoning.	There was no confirmation of poisoning by organophosphates. Enzyme levels were measured only on the first day(<24 h), day 3 and day 15. No specification on prediction of IMS.
Colak S	2014	Retrospective cohort study	71, 67 recruited	Done	No	Serum choline esterase level, serum blood glucose levels	Initial measurement of SAchE and serum glucose levels maybe of a predictive value in determining IMS.	Patients were not assessed by the researchers. The whole research was based on early medical records.
Aygun D	2002	Prospective cohort study	32		Yes	Serum AchE	In the acute stage SAchE supports the diagnosis of OP poisoning but does not show a significant association with the severity of the poisoning.	Enzyme levels were measured only on admission. No sequential measurements were taken.
Aygun D	2007	Retrospective cohort study	47		Yes	Serum creatinine kinase, aspartate amino transferase	The serum muscle enzyme levels measured within the first 24 h does not predict the occurrence of IMS.	There was no confirmation of poisoning by organophosphates. Patients were not assessed by the researchers. AchE levels were not measured.
Dandapani M	2003	Prospective cohort study	19		No	Erythrocyte AchE	Severe and prolonged EAchE inhibition associated with oxidative stress may contribute to the development of IMS.	There was no confirmation of poisoning by organophosphates.
Lin C L	2004	Prospective cohort study	42	Done	No	Plasma amylase	Elevated plasma amylase levels are related to the development of respiratory failure.	The study comments only about the respiratory failure and not about intermediate syndrome.
Liu J H	2008	Retrospective cohort study	82		No	Blood gas analysis	Acid base interpretation in OP poisoned patients may have a predictor value before hospitalization.	Patient selection bias. The patients were not assessed by the researchers but medical records were used. No specification on prediction of IMS.
	Neurophysiological							
De Wilde	1991	Case report	1	Done	Yes	Plasma choline esterase levels	EMG revealed a fade on tetanic stimulation on day 7 which was absent on day 19 indicating a possible post synaptic block	Only one patient was tested.
De Bleecker	1992	Case report	1		No		EMG he did on the patient revealed marked decrements at low rates of repetitive nerve stimulation (RNS) and increments at high frequencies	Only one patient was tested
De Bleecker	1993	Prospective cohort study	Total = 19 IMS = 8		No		RNS initially demonstrated decrement and then increment with final normal response over the course of IMS suggesting a combined	Only 8 patients were investigated. Inadequate sample size.

and 75% of those deaths were related to cardiovascular causes. In the respiratory acidosis group 50% of the patients died following respiratory failure. The conclusion was that acid base interpretation may be effective in quick diagnosis of the outcome of OPI poisoning with regard to respiratory failure (Liu et al., 2008). The types of OPI ingested by the patients were not specified in the study. Again they have retrospectively assessed only the available patient records dating back to nine years, which can lead to a selection bias. Also they have not specified about the possible prediction of IMS but were more focused on predicting mortality. Total number of deaths was 22. 11/22 deaths were due to respiratory failure associated with OPI poisoning while the other 11 deaths was attributed to other causes like cardiovascular problems.

Overall reduction of enzymes EAchE, SchE, BchE and SAE has a modest predictive ability of respiratory failure but their predictive ability of IMS is unclear.

4.3. Prediction based on neurophysiological markers and methods

Neurophysiological testing of organophosphate poisoned patients and research related to it is very minimal in literature and only 6 articles were found of which 3 were case reports.

In 1991 a case report was published indicating a possible post synaptic neuromuscular junctional block in a patient with IMS. In the electromyography (EMG) recoding done on this patient there was a fade on tetanic stimulation conducted by a surface electrode on day 7 which was absent on day 19 on the muscle abductor digiti quinti (De Wilde et al., 1991).

A case report published in 1992 and a prospective study published in 1993 by De Bleecker states that the EMG recordings revealed marked decrements at low rates of repetitive nerve stimulation (RNS) and increments at high frequencies (De Bleecker et al., 1993, 1992b). The conclusion of these studies was that in IMS a combined pre and post synaptic NMJ block is seen (De Bleecker et al., 1993).

Another study done in 1998 by He et al. revealed that 5/7 patients showed a similar decrement pattern at 20 Hz in RNS. This was improved when myasthenia associated with IMS improved further confirming that neurophysiological studies may be the key in early diagnosis of impending IMS. Here again the RNS results were compatible with a post synaptic neuro-muscular junctional block (He et al., 1998).

Another case report was published by Sedgewick and Senanayake in 1997 where they had conducted both RNS and single fibre electromyography (SFEMG) on a 28 year old female who had ingested 60 ml of dimethoate. The patient had gone in to IMS in day 3 and was ventilated until day 15.Neurophysiological studies were conducted on the patient on 7th, 14th and 18th post ingestion days. Patient had recovered completely by day 21 and all the tests were normal on day 18th, including nerve conduction tests done on ulnar and median nerves bilaterally. RNS was done on ulnar nerve at wrist on abductor digiti minimi. On day 7 a single stimulus produced a repetitive discharge but subsequent discharges did not. At 0.5 Hz all discharges produced repetitive discharges but not at 3 Hz or above. No decremental responses were seen even up to 50 Hz even after one minute of exercise or 10 s of continuous discharge. However, on the SFEMG done on extensor digitorum communis showed a borderline increased jitter in 2 pairs. This was markedly seen in the frontalis muscle on day 7 where 12/17 pairs showed increased jitter values with 10% blocking of fibres. This was compatible with the possible theory they produced about neuromuscular junctional blocking in organophosphate poisoned patients affected by IMS (Sedgwick and Senanayake, 1997).

The most recent comprehensive study done on this regard was published in 2008. The researcher had assessed 78 patients prospectively with daily clinical examination and RNS. Ten patients went into IMS and 5 of them required ventilation. RNS was done on median and ulnar nerves on both upper limbs at 1, 3,10,15,20 and 30 Hz. All 10 patients showed progressive RNS changes correlating with the severity of IMS. A decrement-increment pattern was observed at intermediate and high frequencies preceding the development of clinical signs of IMS. With the onset of the clinical symptoms a similar pattern was observed even at low frequencies. At high frequencies a repetitive fade or a severe decrement was seen. This severe decrement was seen in 4/5 patients who developed respiratory failure. Thirty patients had less severe weakness with RNS showing decrement-increment or a combination of decrement-increment and repetitive fade but not a severe decrement indicating that the IMS is a spectrum disorder. The conclusion was that RNS is a useful tool in identifying possible high risk patients of IMS and associated respiratory failure (Jayawardane et al., 2008, 2009). Again in this study, confirmation of the OPI poisoning was based on history and clinical features only. Furthermore the changes in RNS were not described in a time frame which would have been more beneficial.

Based on the available literature on neurophysiological testing of OPI ingested patients, it is clear that RNS and SFEMG have definite changes which precede IMS.

The study results are summarized in Table 1.

Table 1 (*Continued*)

Author	Year of Publication	Type of Study	Number of Patients	Confirmation of OPP	Acknowledment of ingestion time	Enzyme assays/blood Ix done	Conclusion	Limitations
							pre and post neuro-muscular junctional dysfunction.	
Sedgwick E M	1997	A case report	1		Yes		Findings of RNS and SFEMG done on the patient are compatible with a neuro-muscular junctional block.	Only one patient was examined.
He F	1998	Prospective cohort study	272 IMS:21		Yes	Blood AchE	RNS and ENMG changes indicate a post synaptic neuro-muscular junctional block.	RNS and ENMG were done only on 7 patients.
Jayawardane P	2008	Prospective cohort study	78 IMS: 10		Yes		Characteristic changes in RNS, preceding the development of IMS, help to identify a subgroup of patients who are at a higher risk of developing respiratory failure. Further on the RNS changes indicate that IMS is a spectrum disorder.	AchE levels were not measured. The changes in RNS was not shown in a time frame in par with the progression of the disease.

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4.4. Possible prediction of IMS with single fibre electromyography (SFEMG)

Even though RNS as a predictor of IMS has been studied, the role of SFEMG is yet to be studied which may become another useful tool in early prediction of IMS while understanding the underlying derangement of the neuro-muscular junction (NMJ) in OPI poisoned patients who might go into respiratory failure.

The possibility of detecting changes in SFEMG were extensively described by Sedgewick and Senanayake in a single case study and it will be beneficial if positive results are obtained by conducting similar SFEMG on multiple patients with IMS (Sedgwick and Senanayake, 1997). A pilot study done using this method has shown promising results (Weerasinghe et al., 2014).While the electrophysiological aspects of delayed neuropathy are best characterized, those of cholinergic crisis and intermediate syndrome remain very little studied. The persistence of acetylcholine in the synaptic cleft would explain the multiple motor responses to a single stimulation during the crisis (Rafai et al., 2007).

Single-fibre electromyography (SFEMG) is a selective electromyography (EMG) recording technique that helps in the identification of action potentials (APs) from individual muscle fibres which was established by Stalberg and Eskedt in the 1960s, and is of proven value in the diagnosis of neuromuscular disorders, especially myasthenia gravis as this technique directly assesses the neuromuscular junction. It has proved to be the most sensitive technique in detecting a neuromuscular-junctional transmission defect in comparison to the tensilon test, repetitive nerve stimulation, and acetyl choline receptor antibody estimation (Juel, 2012). The selectivity of the technique results from the small recording surface of the needle which is 25 μm in diameter, with an exposed port on the side of the electrode 3 mm from the tip. Practically a concentric needle can be used as well (Kokubun, 2012; Papathanasiou and Zamba-Papanicolaou, 2012; Stalberg, 2012). At a given time two or three muscle fibre action potentials will be recorded with a concentric needle and each fibre action potential can be abstracted separately to study its individual characteristics such as fibre density and the neuromuscular jitter(Stalberg, 2012). When neuromuscular transmission is sufficiently impaired, nerve impulses fail to elicit an action potential and this is called 'blocking' which usually happens when the jitter is markedly prolonged, with MCD >100 microseconds (Selvan, 2011).

5. Conclusion

Ingestion of OPI compounds still remains a worldwide problem and is associated with a high mortality especially related to IMS. Available literature on probable predictors of IMS is minimal.

Possible prediction of the mortality in these patients may be done using clinical scoring systems, though an agreement on which scoring system to be used is still not clear. Most studies mainly focus on prediction of respiratory failure rather than IMS. However, in one study the risk of IMS is found to be higher with advancing age and in patients who present with GCS score <10 or PSS score >2 (Indira et al., 2013).

Low erythrocyte acetylcholine esterase levels and increased plasma amylase levels are associated with impending respiratory failure and subsequent IMS. But Serum acetylecholine esterase levels are only supportive in confirming the diagnosis of OPI poisoning. Its predictive ability of IMS is controversial. Muscle enzyme levels measured in the initial stages has no value in predicting IMS.

As IMS is a sequelae of nicotinic receptor impairment at the neuromuscular junction with persistently elevated acetylcholine in the synaptic cleft, the best predictors are those which assess the neuromuscular junction itself rather than assessing clinical or biochemical factors. Based on the available literature on neurophysiological testing of OPI ingested patients, it is evident that RNS and SFEMG is an open area for research to predict IMS. But only a few case reports are available on possible prediction of IMS by SFEMG which is a promising area of further research.

RNS has been studied extensively which shows a characteristic decrement- increment pattern that precedes IMS.

Even though neurophysiological methods such as RNS and SFEMG remains a good method for screening IMS in OPI poisoned patients, these methods require special equipment stationed within hospitals and specially trained personnel to operate them. Therefore such facilities need to be improved in hospitals. However this can prove to be difficult with limitation of funds for such purposes, especially in developing countries.

As prediction of IMS is of utmost importance to countries like India and Sri Lanka where a higher incidence of OPI poisoning is recorded annually, novel techniques to predict IMS become crucial. As developing countries most of them has lot of financial constraints and limited ICU care facilities to manage patients who require ventilation following respiratory paralysis. This justifies the need for further research in this regard to identify a possible bio marker, using clinical, biochemical or electrophysiological parameters to triage patients selectively and manage high risk patients optimally with the limited number of facilities available to reduce high morbidity and mortality associated with OPI poisoning.

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The authors have no conflicts of interest to disclose.

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