Original Article

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Anemia, Iron Deficiency Anemia and Lead Poisoning in Children with Opioid Toxicity: A Study in North East of Iran

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Abstract

Background: Opium is a new source of lead and considered as a cause of lead poisoning. As anemia and lead poisoning affect growth and behavior negatively, their timely prevention, diagnosis, and treatment are essential. The aim of thi study is evaluation of the prevalence of anemia, iron deficiency anemia, and lead poisoning in children with opioid toxicity.

Materials and Methods: In this cross-sectional study, 150 children admitted to the pediatric poisoning unit of Imam Reza hospital, Mashhad, Iran from May 2015-2016 were divided into two groups of methadone/tramadol and raw opium toxicity. For each child hematocrit, hemoglobin, RDW (red blood cell distribution width), MCV (mean corpuscular volume), CRP(C-reactive protein), and blood lead level (BLL) were tested. One hundred children without opioid toxicity from a simultaneous study were considered as control group and compared with our patients regarding BLL.

Results: The patients' mean age was 33.08±33.35 months. The prevalence of anemia and lead poisoning was 40% and 83.3%, respectively; neither indicating a significant difference between the M/T and opium groups (p=0.241, 0.227). On the other hand, 125(83.3%) and 63(63%) cases and controls had lead poisoning (BLL>5µg/dl), respectively, showing a significant difference (p<0.001). Lead poisoning was not significantly different between the controls and the cases under 2 years of age (p=0.085).

Conclusion: A single episode of opioid toxicity does not result in anemia. However, a significant difference was observed between the cases and controls regarding lead poisoning. Although the BLL in the cases under two years of age was higher than the controls, the difference was not significant.

Keywords: Iron deficiency anemia, Lead poisoning, , Methadone, Opioids, Tramadol

Introduction

Anemia is a common phenomenon worldwide with a higher prevalence in developing countries. More than one fourth of the world's population suffers from anemia while iron deficiency anemia (IDA) accounts for half of such cases. It is mostly seen in preschool-aged children and women (1). Its prevalence was reported as 71% among 6-36 month-old children from Kenya (2). In another study from Pakistan, the prevalence of IDA in preschool children was 82.7%; the same figure was 62.3% in school-aged children (3); 33% of adolescents in Nepal also suffer from anemia (4). In Iran few studies have been performed in this respect; in one study conducted in the south-west of Iran, the rate of anemia was 43.9% while IDA was reported as 29.1% (5). Based on several studies psychomotor disorders and delayed complications of IDA in case of non-treatment may be stabilized and converted into irreversible types (6). In a study by Lozoff et al., the behavioral and mental score of 12-23 month-old children with IDA treated with iron improved after 3 months whereas in cases with delayed or severe anemia, the latter score did not

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improve even following treatment (7). Therefore, timely prevention, early diagnosis and treatment of anemia in children are of great importance.

On the other hand, the rate of poisoning among children is quite high in Iran; around 1000-1200 new cases in the pediatric age group are admitted in Mashhad annually. Among all poisonings, over 700 cases in 2013. Opioids had the highest prevalence (>50%). In a study conducted on the lab data of such children, almost in 100% of cases with opioid toxicity, anemia was present. In this respect, around 2 million cases of poisoning are reported annually in the United States and around 50% occur in children < 6 years of age. Based on recent research, one of novel source of lead toxicity are opioids (8,9) and therefore opioids can be considered as one of the causes of lead poisoning. From the biochemical aspect, lead has a low melting point besides the ability to form stable compounds, resulting in huge interest in its use in the production of many industrial products. Due to such properties lead is added to opioids as an impurity.

In a study conducted in Tehran, among the 240 patients with lead poisoning, 25 were caused due to opium consumption (8). Moreover, lead poisoning is one of the underlying causes leading to anemia in children and still remains as a global health problem (10). Reported statistics from Europe and the US show a decrease in lead blood levels among children in such areas, mainly due to controlling measures for lead level in fuels, paints, foods, and drinking water (11).

The blood lead level (BLL) is the gold standard for assessing the effects of lead on health. Although the threshold level in which biochemical disorders occur and clinical and subclinical symptoms appear is not yet defined; the Centers for Disease Control and Prevention (CDC) have recently suggested 5µg/dL as a reference value for identifying children at risk of lead poisoning who have lived in environments with the risk of lead exposure. It is worth noting that lead poisoning may still occur below this level and there is no immune level for lead; it also clarifies the measurement accuracy limitations of the current clinical lab techniques (12). Taken together, in 2005 the normal BLL was defined as 0µg/dL by the WHO (world health organization).

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Nevertheless, high blood lead levels reduce the life span of red blood cells, probably leading to hemolytic anemia. However, most cases of anemia in children with lead poisoning are caused due to other etiologies such as iron deficiency and hemoglobinopathies (12).

This study was aimed at evaluating the rate of anemia, IDA, and lead poisoning in children admitted to the pediatric toxicology ward, so that better therapeutic measures can be suggested for the considerable population of anemic children.

Materials and Methods

This study was performed on 80 patients. In this study, 150 children aged 4 days to 13 years with raw opium or methadone/tramadol toxicity, visiting the emergency and pediatric poisoning units of Imam Reza hospital, Mashhad, Iran from May 2015 to 2016 were recruited. The sampling method was simple and non-randomized.

All children with a history of opioids usage or signs of opium consumption in their clinical examination, confirmed with a urine test for opium and its derivatives, methadone and tramadol, were enrolled.

Children with known hematologic disorders, malnutrition, malignancy, history of trauma or hemorrhage in the past three months, fever and infection and liver or kidney disease were excluded from the study. Prior to study entrance an informed consent was obtained from each child's parent/guardian. The study protocol was approved by the Ethics Committee of Mashhad University of Medical Sciences.

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A specially designed questionnaire containing demographic data was filled in for each participant. A 5cc blood sample was then obtained for certain lab tests including hematocrit, hemoglobin, mean corpuscular volume (MCV), Red blood cell distribution width (RDW), C-reactive protein (CRP) and the blood lead levels. Cases with a BLL>5µg/dL, were considered as lead poisoning. IDA was confirmed in children with hypochromic microcytic anemia and a high RDW; such cases were treated under the supervision of a pediatric hematologist.

The case group consisting of 150 children was divided into two subgroups: Raw opium (n=56) and Methadone/Tramadol (n=94). Accordingly, 100 children without opioid toxicity recruited in a simultaneous related project were used as the control group and their BLL was compared with the case group. The main outcome measure was the rate of anemia, IDA, and lead poisoning among children with opioid and methadone/tramadol toxicity visiting the Pediatric Emergency Unit of Imam Reza Hospital.

The collected data were then analyzed by SPSS (ver. 15). Chi-square test was used for comparisons of qualitative data. A P<0.05 was considered as statistically significant.

Results

In total, 150 patients were studied; 56 with opium poisoning and 94 with methadone/tramadol poisoning. The patients' mean age was 35.08±33.35 months (range: 4 days-13 yrs); in total 80 (53.3%) cases were male including 33 (58.9%) cases in the opium group and 47 (50%) in the methadone/tramadol group. Chi-square test showed no meaningful difference between the two groups regarding sex (p,=,0.289).

The most common age group with methadone/tramadol poisoning was the 24-60 months age group whereas for opium poisoning it was the 6-24 months age group; the difference between the two groups was statistically significant (p<0.001). In total, 75 (79.8%) cases of the methadone/tramadol group and 43 (76.8%) of the opium group lived in the city while the rest lived in the village; no significant difference was found between the two groups regarding the residential location (p=0.665).

Given the fathers' educational status, under diploma degree was the most common, yet indicating no meaningful difference between the two groups (p=0.817). The same result was obtained for the mothers' educational level (p=0.681). Furthermore, 10 (10.6%) and 7 (12.5%) of cases in the methadone/tramadol and opium groups had growth retardation, respectively; again indicating no significant difference between the two groups (p=0.792).

The rate of anemia and the morphology of red blood cells (RBC) in the two studied subgroups is presented in Table I; no meaningful difference was observed between the two groups accordingly (p=0.241, 0.752). Table I also demonstrates the rate of different types of anemia in the two mentioned groups. The rate of lead poisoning was 81 (86.2%) and 44 (78.6%) in the methadone/tramadone and raw opium subgroups, respectively; it demonstrated no significant difference (p=0.227). However, when comparing the case and control groups, a significant difference was achieved in this respect (p<0.001). Among the under 2-year-old children, 55 (75.3%) had lead poisoning. This figure was 63 (63%) among the controls; revealing no significant difference between the two groups (p=0.085).

Furthermore, 10 (17.9%) cases in the opium group and 11 (11.8%) in the methadone/tramadol group had a positive CRP test; yet it showed no meaningful difference between the two groups (p=0.306).

The mean BLL in anemic and non-anemic children was 9.42±3.8 and 8.29±4 µg/dL, respectively; T-test revealed no significant

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difference (p=0.09). Moreover, Pearson's correlation coefficient showed that with an increase in the BLL, the Hb level decreases, indicating a weak meaningful correlation between BLL and Hb (r=-0.2, p=0.02). This test also showed no significant association between BLL and MCV (r=-0.13, p=0.1).

Table I: Comparison of anemia rate, type of anemia and red blood cell morphology between the two studied groups: methadone/tramadol and opium

Variable/group		Methadone/ tramadol	Opium	p-value
anemia		No. (%)	No. (%)	0.241
	Yes	41 (43.6)	19 (33.9)	
	No	53 (56.4)	37 (66.1)	
	Total	94 (100)	56 (100)	
red blood cell morphology in anemic cases	Normochrome microcytic	21 (51.2)	11 (57.9)	0.752
	Hypochrome microcytic	10 (24.4)	3 (15.8)	
	Hypochrome normocytic	10 (24.4)	5 (26.3)	
	Total	41 (100)	19 (100)	
type of hypochromic or microcytic anemia	IDA	14 (63.6)	6 (66.7)	
	IDA+THAL	4 (1.2)	3 (33.3)	
	THAL	4 (18.2)	0 (0)	
	Total	22 (71)	9 (29)	

Table II: Comparison of lead poisoning prevalence between the study groups

Group	Lead poisoning		P-value
	Yes	No	0.227
methadone/ tramadol	81 (86.2)	13 (13.8)	
opium	44 (78.6)	12 (21.4)	
study	125 (83.3)	25 (16.7)	<0.001
control	63 (63)	37 (37)	

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Discussion

Poisoning is a very common phenomenon among children in Iran especially Mashhad where opioid toxicity accounts for the majority of cases. In a retrospective study on the lab data of such children anemia was present in 100% of opioid toxicity cases; opioids are also considered as a new source of lead poisoning (8, 9). Based on the findings of the current study and despite no significant difference, the rate of opioid toxicity was slightly higher among boys in comparison to girls (53.3% vs. 46.7%); this finding is similar to other studies in this field (13, 14) and may be due to the higher energy, activity and curiosity of boys (15).

When considering the age of the studied children, 85% of the methadone/tramadol group were under 5 years of age, similar to 91% of the cases in the opioid group. In a study conducted in Zahedan in 2012, 86.8% of children with opioid toxicity were less than 5 years old (16). In another recent study from Isfahan, Iran 89.5% of such children were < 6 years of age (17).

Such findings further emphasize the role of parents in this particular age of children and the need for special parental training in this respect. Moreover, the lower peak age of the opium group (6-24 months vs. 24-60 months) may be due to the fact that children at this very young age are incapable of consuming opioids themselves and the opium is mostly given by the parents in this age; whereas for methadone and tramadol, the children usually take such drugs by accident.

On the other hand, around 78.7% of the opioid toxicity cases lived in the city. Mothers living in cities have more responsibilities and are mostly employed which affects their dedicated time and attention to their children. In addition, the accessibility of opioids is higher in cities as well as accessibility to hospitals which both may affect the higher rate of poisoning in cities (18).

The most common educational status of the parents was under diploma degree. Petridou et al. in 1996 concluded that the educational status of the mother cannot be regarded as a risk factor in this respect (19). However, in Goudarzi et al. study in Shiraz, the rate of opioids consumption and dependence among adults was significantly higher among individuals with an under diploma degree (20). This was also stated in Ahmadi et al. study in 2007 (21).

In the present study no significant difference was observed between the methadone/tramadol and opium toxicity groups in terms of growth retardation (p=0.792); it had a prevalence of 11.3% among the study population revealing no higher rate of growth retardation for opioid toxicity. In the study by Ziaoddini et al. in 2010 on 899035 children, growth retardation was reported in 12.7% (22). When comparing the rate of anemia, again no meaningful difference was observed (p=0.241). Keykhaee et al. (5) reported anemia in 43.9% of their studied children, whereas anemia had 49.2% prevalence in a recent study from Nigeria (23). Despite no control group for anemia comparison, the total rate of anemia was 40% in the current study, consistent with the above mentioned studies. It further clarifies that a single episode of opioid toxicity cannot cause anemia in children.

Moreover, among children with opium and methadone/tramadol toxicity 44 (78.6%) and 81 (86.2%) had lead poisoning respectively, revealing statistical insignificance. However, a meaningful difference was observed between the case group and the controls in this respect (83.3% vs. 63%) Given that all children in the control group were under 2 years of age, a higher but insignificant rate of lead toxicity was obtained among under 2-year-old cases

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compared to controls (75.3% vs. 63%). Salehi et al. also reported a higher BLL in those suffering from addiction and opiate dependency (24). Amiri et al. and Hashemi et al. have also confirmed these findings (25, 26).

In the current study a decrease in hemoglobin (Hb) level was observed with a rise in BLL, indicating a weak meaningful correlation. The exact mechanism causing lead poisoning as a result of opioids contamination with lead is yet not clear, although it is already known that long and chronic opioid usage is essential (27). In the present study despite our expectation, the rate of lead poisoning was higher among children with methadone/tramadol toxicity rather than opioids, highlighting the need for further studies to outline the related underlying mechanisms. However, it should be noted that the mean age of the opium group was lower than the methadone/tramadol group; therefore, the latter group had a longer exposure period to environmental pollutants such as lead, possibly leading to a higher poisoning rate in this group. On the other hand CRP is one of the most important inflammatory factors in the body and it seems that lead exposure can stimulate the immune system resulting in positive CRP levels (28-30). Moreover, increased BLL can cause oxidative stress, eventually leading to the activation of other pathways affecting tumor nacrosis factor- α (NF-α) and Interleukin-1 (IL-1), and enhancing the production of CRP in the liver (31).

This study revealed that 40% of children with opioid toxicity also suffered from anemia. Regarding the similarity of anemia prevalence with other studies without opioid consumption, it can be concluded that a single episode of opioid toxicity cannot result in anemia in children. Moreover, the difference in the rate of lead poisoning between the groups with and without anemia was not statistically significant; this may be due to the high rate of anemia in our region (40%). Furthermore, in children with opioid toxicity, the BLL was significantly different from the controls. In children under 2 years, although not significant, the BLL was higher in the cases compared to controls.

The main limitation of the present study was not measuring the ferritin level, as a diagnostic test for IDA. This was due to the early discharge of patients or not visiting the clinic after discharge. As opioids are usually given to children by their parents for treating infections, ferritin level measurement following recovery from different infections is highly recommended in future studies.

Conclusion: Prevalence of anemia and lead poisoning was 40% and 83.3%. One episode of opioid toxicity does not cause anemia. However, a significant difference was observed between the study and control group regarding lead poisoning. Although BLL in the cases under two years was higher than the controls, the difference was insignificant.

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Conflict of interest

Authors have no conflict of interest.

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