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Nyaope and anaesthesia

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Introduction

Nyaope, a novel psychoactive substance, has been used increasingly in South Africa since 2000. It is a mixture of low-grade heroin, cannabis products, antiretroviral drugs and other materials used as bulking agents.[1] The chemical makeup of nyaope varies geographically within South Africa according to the availability of raw materials and demand patterns from regular users. It is also known by various other names, including whoonga, pinch, unga and sugars. It is unique to South Africa and, until recently, was not classified as illegal. It was only with the amendment of the Drugs and Trafficking Act of 2014 that nyaope was classified as an illegal substance. Despite this, the situation has evolved rapidly since 2015, and anecdotal evidence suggests that in black townships, Nyaope may be the drug most frequently used.[2] This situation has received surprisingly little attention as a national issue and there is a lack of formal studies despite its widespread use.

With the global opioid crisis, attention is largely focused on the opioid epidemic within high-income countries such as the United States. Prescription and non-prescription opioid use has been increasing in many African countries, particularly in South Africa. Heroin is the most commonly abused illicit opioid in South Africa.[3] Several factors have led to the increased availability and affordability of heroin in South Africa. These include increased production of opium in Afghanistan as well as an increased significance in the southern trafficking route of heroin out of Afghanistan bound for the lucrative European and North American markets. This has resulted in a thriving regional heroin economy in South Africa and has created new drug markets in rural and socially disadvantaged communities.[4] Today heroin is sold and used in all major South African cities, large and small towns, rural areas as well as in large populations of homeless people.[5] The latest South African community epidemiology network on drug use (SACENDU) surveillance report indicates that heroin (including data for nyaope and whoonga) is the primary substance of use for 37% of patients admitted to specialist substance use treatment centres in the northern region and for 29% of patients in Gauteng (Table I). Data collected from SACENDU, although valuable, is limited as it only reflects those users who seek treatment.

Factors predisposing to drug use include unfavourable social conditions like poverty, unemployment, and a lack of recreational

Table I: Primary substance of use (%) for all persons and persons under 20 years – selected drugs[6]

	Age	WC	KZN	EC	GT	NR[a]	CR[b]
# Centres (*n*)	All	36	9	4	34	7	4
# Persons admitted (*n*)	< 20	2 433	723	386	6 226	958	212
Alcohol	All	18	33	27	9	14	30
	< 20	10	8	1	4	6	2
Cannabis	All	24	23	22	27	37	24
	< 20	52	64	50	55	75	59
Methaq. (Mandrax)	All	7	2	5	3	< 1	4
	< 20	7	-	1	2	1	4
Cocaine	All	3	13	4	3	3	5
	< 20	1	5	2	3	-	-
Heroin*	All	7	23	2	29	37	7
	< 20	8	12	1	11	8	2
Methamphetamine	All	35	2	36	17	6	26
	< 20	20	1	43	15	4	28

*Includes data relating to nyaope and whoonga[1]; [a]Northern region (MP & LP), [b]Central region (FS, NW, NC)

Table II: Recommended terminology regarding substance use[7]

Say this	Not this	Here's why
Terminology regarding substance use		
Substance use disorder; (insert specific substance: opioid, cocaine, alcohol, etc.) use disorder	Drug abuse/dependence Substance abuse/dependence.	The diagnostic terms "substance abuse" and "substance dependence" described in the DSM-IV have been combined in the DSM-5 into "substance use disorder"
Intoxicated or in withdrawal	Strung out, tweaking, high, drunk (and other colloquial substance-specific terms)	Uses medically accurate language to describe the state of intoxication or withdrawal from a substance
Terminology regarding persons		
Person with a substance use disorder	Substance/drug abuser, addict, junkie, druggie, stoner, alcoholic, drunk (and other colloquial substance-specific terms)	Uses person-first language, as individuals are not defined solely by their substance use
Person who uses (insert specific substance: opioid, cocaine, alcohol, etc.)	Drug user, heroin user, drinker, crackhead, pothead, drug-seeking (and other colloquial substance-specific terms)	
Person who injects drugs (PWID)	Injection drug user	
Treatment was not effective Patient in need of more support/higher level of treatment	Patient who failed treatment Noncompliant, nonadherent	Referring to the treatment not meeting the needs of the patient or the patient needing a higher level of treatment, rather than the patient failing

facilities. This, together with the fact that nyaope is relatively cheap to buy, with an average price of R30 a hit, seems to be fuelling the use of nyaope in our most disadvantaged communities. Nyaope is reported to be highly addictive and withdrawal symptoms are severe. There is also a severe lack of drug rehabilitation services in the public sector as well as a high relapse rate in those who have managed to access rehabilitation services.[2] All of these factors combine to keep the nyaope user trapped in a vicious cycle of ongoing use of the drug with devastating physical, mental, social, and economic consequences. As anaesthetists, particularly those of us working in the public sector, we can expect to encounter patients using nyaope on a more frequent basis. We therefore need to understand the implications of the use of nyaope on perioperative management, in order to provide safe and effective anaesthesia and analgesia to this group of patients.

Terminology

For much of history, substance use has been viewed as a moral failing for which individuals themselves are to blame. In recent times addiction has come to be understood as a medical disorder. Clinical terminology has shifted, along with a growing awareness of the harm of stigmatising language in medicine. The American Academy of Pediatrics (AAP) has provided recommendations regarding medically accurate, person-first, non-stigmatising terminology.[7] It behoves us as anaesthetists to use this updated terminology when interacting with our patients.

Composition of nyaope

Nyaope is a fine brown powder due to its mixture with soil, sand or, in some cases, cement powder, in order to disguise the underlying white powder as seen in Figure 1.[8] It is usually wrapped in marijuana leaves and smoked. An increasing number of users dissolve the powder and inject it, which brings in a whole range

Figure 1: Illustrative sample of nyaope[1]

of complications related to injectable drug use.[9] Being a cocktail drug, it is not always certain what all the ingredients are, as these vary from different sources and because it is not manufactured according to specified standards. The effect varies according to the composition, as well as the number and amounts of substances in the specific cocktail. Because new compounds are continuously introduced, there is less confidence in the management of nyaope users by professionals. The results of a study done on identifying the composition of various samples of nyaope taken from users in areas surrounding Pretoria are shown in Table III. All samples contained high levels of heroin, mixed with minor quantities of other substances.[8] The challenge is the heterogeneity and constant change in its formula. The drug interactions between the various components of nyaope are reported to increase the toxicity as well as the organ damage that occurs.[10]

Perioperative approach to a patient with nyaope use disorder

Patients who have a substance use disorder may present for surgery in a variety of circumstances including elective surgery

Table III: Constituents of nyaope samples acquired from various townships analysed using two different mass spectrometers[8]

		Constituents identified in Nyaope																	
Area and number of sources	Method	Caffeine	Acetaminophen	Opiate (meconin, methadone:papaverine, Dimenoxitol	Dextromethophan	Codeine/metabolites	Morphine/metabolites	Heroine	Amphetamine/meth-metabolites	Cathine (b OH amphet)	Citroflex A	Duracaine/lidocaine	Anti-retroviral (zidovudine)	Thiofentanyl	Benzitramide (narcotics)	Benzodiazepines	Phenobarbitone	Pipradol (Dopamine reupt)	Moramide narcotics	Fenethyline (stimulants)
Garankuwa (sample 2)	GC	+	+	+	+	+	+	+												
	TOF	+	+	+	+	+	+	+	+											
Soshanguve (sample 1)	GC	+				+	+	+				+								
	TOF	+	+				+	+	+											
Bronkhorstspruit (sample 2)	GC	+				+	+	+			+									
	TOF	+		+			+	+	+	+					+		+	+	+	
Witbank (sample 2)	GC	+	+		+	+	+	+	+											
	TOF	+	+		+			+	+											
Mamelodi (sample 8)	GC	+			+		+	+	+											
	TOF	+		+	+	+	+	+	+	+		+		+						
Springs (sample 1)	GC	+	+		+	+	+	+												
	TOF	+		+	+			+	+						+					
Pretoria central (sample 5)	GC	+	+		+	++	+	+												
	TOF	+	+	+	+			+	+				+			+				
Ramogodu (sample 3)	GC	+						+												
	TOF	+	+				+	+	+	+			+							
Winterveld (sample 2)	GC	Not done due to insufficient samples																		
	TOF	+		+			+	+	+	+					+					
Delmas (sample 2)	GC	+			+	+	+	+												
	TOF	+			+		+	+	+	+										+
Tembisa (sample 4)	GC	Not done due to insufficient samples																		
	TOF	+		+		+		+	+					+	+			+	+	
Sunnyside (sample 9)	GC	+	+			+	+	+												
	TOF	+					+	+	+	+			+	+	+	+				

or acute life-saving situations. Nyaope users, by virtue of their lifestyle, have a higher risk of presenting for emergency surgery related to both sepsis and trauma. Opioid use disorders are associated with substantial morbidity and mortality. Mortality risk is estimated to be 15 times that of the general population.[3] When planning our anaesthetic care, we need to understand the effects of this highly addictive drug and how it impacts the perioperative management of these patients.

Preoperative

Optimal patient care always begins with a careful patient assessment including a thorough history and examination. Collateral history from family or accompanying adults may be extremely helpful, although nyaope users are very often socially isolated and alienated from their families. The clinical management will differ depending on whether the patient is a chronic user, acutely intoxicated or in acute withdrawal. It is therefore important to be able to recognise the relevant signs and symptoms of each of these states. Nyaope is a cocktail drug with significant variability in its composition, but it is generally agreed that it is the heroin component uniformly present in all samples which makes it such a highly addictive and dangerous drug. Heroin is a synthetic opioid known as diacetylmorphine. It is rapidly hydrolysed to 6-monoacetylmorphine (6-MAM), which in turn is hydrolysed to morphine. Both heroin and 6-MAM are more lipid-soluble than morphine and therefore enter the brain more readily.

Signs and symptoms of opioid intoxication[11]

- Euphoria, profound relief from anxiety and tension, followed by apathy.
- Initial mild, brief increase in energy, followed by psychomotor retardation
- "Nodding" – state between arousal and sleep, where the individual is rousable.
- Pupillary constriction.
- Hypoactive bowels, constipation.

- Slow regular respiration, decreased coughing, risk of respiratory depression.
- Slurred speech.
- Impaired judgement, concentration, memory.
- Dulling of pain.
- Difficulty with passing urine.
- Nausea and vomiting.
- Sweating, warm flushing of the skin, itching.
- Dry mouth.
- Rarely convulsions.
- Large doses of heroin may result in a potentially lethal overdose.

The onset and duration of withdrawal depend on the half-life of the abused opioid. For heroin, withdrawal will start 6–12 hours after the last dose was taken. Heroin withdrawal peaks at 36–72 hours and usually lasts for a period of five to ten days. Nyaope users present with a unique withdrawal feature of severe unbearable abdominal cramps. This drives the user to desperately seek the next fix. There have been reports of life-threatening abdominal complications that require surgery such as perforations due to mesenteric artery ischaemia.[10] This is thought to be due to the complex nature of the combined effects of the various possible constituents of nyaope. A study done looking at the drug interactions in the constituents of nyaope, showed that there are extensively shared metabolic pathways between the various major and minor constituents of nyaope. This leads to a longer half-life for each of the drugs with a synergistic effect leading to a longer-lasting euphoria as well as synergy in the adverse effects of these combined drugs.[10] Further research is needed to understand how metabolic pathways and drug interactions impact the clinical presentation in users.

Signs and symptoms of opioid withrawal[11]

- Looks like a "flu-like" illness.
- Abdominal cramps.
- Anxiety, craving, irritability, dysphoria, fatigue.
- Hot and cold flushes, muscle aches, nausea, and sweating.
- Restlessness.
- Increased blood pressure and heart rate.
- Dilated pupils.
- Vomiting, diarrhoea, lacrimation, and rhinorrhoea.
- Muscle spasms and pilo-erection.

Chronic effects of the use of nyaope

Psycho-social

Important risk factors for the use of nyaope include unemployment, male gender, younger age, non-completion of secondary school, prior substance use, co-substance use (most commonly cannabis, tobacco and alcohol), being HIV-positive, stressful home environments and other social factors.[12] Nyaope addiction tends to lead to financial difficulties and damaged family relationships, which in turn leads to social stigmatisation and criminality.[12] The unfavourable social environment, high unemployment rates and unstructured life promotes continued use.[9] Users present with slow and slurred speech, slow kinetic movements and poor hygiene. Radiological assessments show that nyaope users display extensive grey matter atrophy in the regions of the brain involved with impulse control, decision making, social and self-perception, and working memory.[13] Psychiatric problems are common in this population. Comorbidities include mood disorders, anxiety and personality disorders, post-traumatic stress disorder, and substance-induced psychosis.[3]

General

Nyaope users do not eat healthily and do not have fixed eating patterns. This is due to poor social circumstances, financial constraints and to the appetite suppressant effect of nyaope. Chronic users are invariably severely malnourished. They also display very poor personal hygiene and often present with feelings of irritability, insomnia, involuntary jaw clenching and tooth grinding.[10] Vascular access may be challenging due to scarring and damaged veins.

Infectious complications of injecting drugs

Nyaope is sold in powder form, and although in its early stages, it was smoked by rolling it with cannabis, an increasing number of users dissolve the powder in water and inject it. This brings in a whole range of infectious complications related to injectable drug use.[14] These include:

- HIV
- Hepatitis B and hepatitis C
- Skin and subcutaneous tissue infections: abscess, cellulitis, and necrotising fasciitis
- Pneumonia: typical community pathogens, aspiration, *Klebsiella pneumonia*, tuberculosis, AIDS-associated opportunistic infections, pulmonary septic emboli, and lung abscess formation
- Cardiovascular: endocarditis, infected pseudoaneurysm
- Central nervous system (CNS): epidural abscess of calvarium and spine, brain abscess
- Lymphatic system: splenic abscess
- Endovascular: mycotic pseudoaneurysm
- Musculoskeletal infections: psoas abscess, septic arthritis, osteomyelitis

A recent study done in South Africa on people who inject drugs found the prevalence of HIV to be 21%. Hepatitis C seroprevalence was 55%, and hepatitis BsAg positivity was 5%.[15]

Airway and lungs

Nyaope users may sometimes present with burn marks around the nostrils and mouth from combustion of the drug. Several factors may compromise the airway as well as oxygenation and

ventilation. Smoking of nyaope leads to impaired pulmonary defence mechanisms, chronic cough, airflow obstruction and an increase in acute and chronic pulmonary infections including tuberculosis. Additionally, toxic adulterants used as bulking agents may cause lung damage such as talcum pneumonitis. Pulmonary oedema may occur in patients who have overdosed on heroin. Aspiration may also occur due to delayed gastric emptying or decreased levels of consciousness.

Cardiovascular

A study done at Chris Hani Baragwanath Academic Hospital found a dramatic rise in the number of patients with infective endocarditis related to intravenous nyaope.[15] This is most likely linked to the new pattern of injecting nyaope as opposed to smoking it. Most of these patients presented late because of delay on the part of the patient as well as late referral and misdiagnosis. *Staphylococcus aureus* was the most common pathogen found.

Drug solutions may also contain ingredients which are not water soluble, leading to particles in the vasculature that can cause inflammation and clot formation and ultimately pulmonary hypertension.

Hepatic and renal

Renal complications from the use of heroin are common and include nephrotic syndrome, acute glomerulonephritis, interstitial nephritis, and rhabdomyolysis. There is a three-fold increased risk of renal dysfunction in heroin users versus non-drug users.[16] Liver dysfunction may be due to viral hepatitis A, B or C and some patients may go on to develop liver cirrhosis and hepatocellular carcinoma. Alcoholic liver damage is also common due to concurrent alcohol use disorder. The major and minor constituents of nyaope share metabolic pathways which leads to synergy in both the euphoric effects of the drug and in its toxicity profile.[10] Toxic adulterants may cause direct renal or hepatic damage.

Chronic medications

Nyaope users who are in recovery might be on chronic opioid substitution therapy. These medications include:[3]

- Methadone: a full mu opioid agonist and NMDA antagonist. Its full agonist properties lead to concerns about toxicity, which include reduced motor function and respiratory depression. Further safety concerns with methadone include cardiac effects (QTc prolongation with a risk of Torsade's du Pointes). Clinicians should be aware of drug interactions that may contribute to QTc prolongation.
- Buprenorphine: a partial opioid agonist and kappa antagonist. It has reduced intrinsic activity, compared with a full agonist, and high receptor affinity.
- Buprenorphine-naloxone combination: this combination is available in South Africa as suboxone.
- Naltrexone: a specific, orally active, long-acting opioid antagonist. It has a high affinity for the mu opioid receptor, without any intrinsic activity and thereby effectively blocks the effect of any administered opioid.

Opioid substitution therapy has implications for the management of perioperative analgesia as well as potential side effects.

Investigations

- Full blood count: to exclude anaemia and look for evidence of infection
- Electrolytes: to assess renal function
- Liver function tests
- Tests for HIV, hepatitis A, B and C
- Urine or saliva drug tests: these should be interpreted in the light of clinical findings, as false positives and false negatives can occur

Intraoperative

Management goals in nyaope use disorder patients include managing acute intoxication if present, preventing or treating opioid withdrawal, and managing pain effectively and safely. Acute opioid intoxication may cause respiratory depression and loss of airway control as well as decreasing anaesthetic and analgesic requirements. In heroin users, perioperative hypotension tends to occur, which may reflect inadequate intravascular fluid volume secondary to chronic infections, fever, malnutrition, and adrenocortical insufficiency. It is important to note that the setting of severe acute pain, as is frequently the case in the perioperative period, is not the time to attempt opioid weaning and detoxification. On the contrary, undertreated pain is a risk factor for the development of chronic pain and persistent opioid use. Preventing or treating withdrawal is crucial in the management of these patients as they do not have access to their usual supply of opioids. Therefore, it is important to provide sufficient opioids to prevent or treat withdrawal, in addition to treating the acute pain. Repeated exposure to exogenous opioids leads to desensitisation of the opioid receptor resulting in tolerance requiring escalating doses of opioids to achieve the desired effect. Long-term users have increased sensitivity to pain caused by opioid-induced hyperalgesia. Chronic opioid use also leads to cross-tolerance to other central nervous system depressants. Higher doses of opioids are usually required to manage pain effectively. Multimodal analgesia is essential, and consideration should be given to the use of local anaesthetics, regional anaesthesia, acetaminophen, nonsteroidal anti-inflammatory drugs, gabapentinoids and alpha-2-adrenergic agonists. The management of acute opioid withdrawal in the perioperative setting includes:

- Acute opioid administration.
- Fluid resuscitation if needed.
- Alpha-2-adrenergic agonists: these agents are particularly useful for treating the sympathetic hyperarousal of withdrawal.

- Adjunctive medications for nausea and vomiting, diarrhoea, anxiety, dysphoria, and muscle cramps: promethazine, loperamide, octreotide, benzodiazepines.

For patients already taking methadone for the treatment of opioid use disorder, their regular dose of methadone in addition to additional doses of perioperative opioids will be required to provide effective analgesia.[17] For patients who are already on buprenorphine, an increase in buprenorphine dosing may be sufficient for mild acute pain. However, for severe acute pain, it is recommended to stop buprenorphine 24–36 hours in advance of surgery and to replace it with a high-potency full opioid agonist.[17] Management of acute pain in patients taking naltrexone poses distinctive challenges, as naltrexone blocks the effect of opioid agonists. For patients on naltrexone requiring surgery and the use of opioids, discontinuation of oral and injectable naltrexone is recommended 72 hours and 30 days respectively, before elective surgery.[17]

Postoperative

Effective pain management and monitoring for and managing withdrawal are critical. The perioperative period is not the time to initiate weaning or attempt rehabilitation. Referral to and coordination with substance use disorder treatment specialists is indicated.

Conclusion

South Africa has not been spared the global opioid crisis. The explosion of the use of nyaope amongst our most marginally and socially disadvantaged communities has created our own unique opioid crisis in the form of low-grade heroin, mixed with an alarming array of psychoactive and toxic substances. Nyaope use disorder is complex and requires interventions at numerous different levels. It behoves us, as anaesthetists, to treat these patients with dignity and to understand this unique disorder and how it impacts safe perioperative management.

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