

Ultra-rapid opioid detoxification: Current status and controversies

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ABSTRACT

Opioid dependence is a major health problem and a cause of increasing concern to physicians and other health professionals worldwide. A crucial first step in intervention is detoxification. Recent trends in medical practice have seen the emergence of newer techniques that claim to accelerate the detoxification procedure and ensure prevention of relapse by rapid induction onto maintenance treatment with opioid antagonists such as naltrexone. This review delves into the theoretical and methodological aspects related to ultra-rapid opioid detoxification (opioid detoxification procedure using opioid antagonists, performed under general anaesthesia or heavy sedation) and discusses the status of the same in light of the available evidence regarding its applicability, safety and effectiveness. Although useful in some respects (especially in completion rates for detoxification and subsequent induction onto naltrexone maintenance), the justification of this procedure lies in (a) the resolution of the ethical conflicts surrounding the procedure and (b) conduction of methodologically sound long-term studies to demonstrate greater efficacy over routine/standard detoxification procedures *beyond* the short-term detoxification period.

KEY WORDS: Opioid abuse, detoxification, anaesthesia-assisted detoxification, ultra-rapid detoxification

Opioid dependence is a complex and difficult-to-treat illness.¹ Its treatment typically involves detoxification and an array of subsequent procedures. Although options other than initial detoxification do exist, for a treatment-seeking opioid-dependent patient, at least in India, the usual first step is detoxification. This is because methadone or levorotary alpha acetyl methadol (LAAM) is not available in India, buprenorphine is available in very low-dose preparations, obtained with great difficulty and cost, and is much more often abused by patients than used therapeutically for substitution or maintenance purposes. Under the circumstances, the reality remains that opioid-dependent treatment-seeking patients in India are *first* detoxified and then moved on to the relapse prevention and rehabilitation procedures. Over the past 20-30 years, innovations have been attempted in the process of detoxification.² One of these, variously known as rapid, ultra-rapid, or anaesthesia-assisted detoxification,³ is now being practised in many countries, and apart from interest, it has also generated significant controversy so as to merit a discussion regarding its current status. The procedure has been recently introduced in India, primarily by private practitioners working in profit-making corporate set-ups, and has often been claimed as showing "100% results" or a "miracle procedure". At the same time, some published research has tried to evaluate the issue in a more objective manner.

Historical Background

Management of the withdrawal syndrome can be subjectively

very distressing for the patient.⁴ The traditional medical approach to the management of this syndrome involves either substitution with a long-acting opioid, e.g., methadone,⁵ and subsequent tapering, or the use of non-opioids, such as clonidine along with adjuncts, viz., analgesics, hypnotics and benzodiazepines. This is often followed by the gradual introduction of oral mu-receptor antagonists such as naltrexone.⁶ It may involve a significant amount of discomfort to patients who often terminate the detoxification process and return to opioid use (especially illicit use). Some opioid-dependent patients may not even attempt detoxification because of their fears of the discomforts of the withdrawal process. Therefore, since the beginning of the 1970s attempts have been made to induce and shorten the opiate withdrawal by clonidine and opiate antagonists.⁷ Blachley et al⁸ were among the first to suggest the use of anaesthesia to make the process of detoxification more humane. This method was first developed by Loimer et al⁹ with patients under anaesthesia and intubation based on earlier rapid detoxification methods published by researchers at the Yale university.^{10,11} Thereafter, several modifications and improvements have been suggested by various groups of researchers in the technique of ultra-rapid opioid detoxification (henceforth referred to as UROD).

Concept

The common underlying themes in all the programmes of UROD are the following:

1. To shorten the detoxification process to a 6-8-hour period¹² by precipitating withdrawal following the adminis-

- tration of opioid antagonists under general anaesthesia.
2. To blunt the awareness of physical discomfort by deep sedation or anaesthesia.
 3. To shorten the time lag between a patient's last dose of opioid and his transfer (induction) onto naltrexone maintenance.

The prelude to this concept was demonstrated in animal research by Rasmussen et al,¹³ who showed that electrophysiological, biochemical and behavioural parameters of opioid withdrawal peak and recover to near baseline within 6 hours of administration of high dose of opioid antagonists to morphine-addicted rats. These reactions involve the nucleus locus coeruleus. However, the actual technique has been developed and used in man without a valid animal model to explore the long-term consequences or effectiveness of the same. As pointed by Spanagel et al,¹⁴ there is no evidence that an opiate antagonist can accelerate the restoration of neurobiological homeostasis after opiate withdrawal. However, the interference of withdrawal signs observed after naloxone-precipitated opiate withdrawal under anaesthesia could reflect a potential pharmacological modulation of withdrawal signs induced by anaesthetic agents.¹⁵ Some studies have shown that the use of anaesthetic agents only temporarily conceals the expression of withdrawal signs with subsequent accentuation of the same.¹⁶ So, it is not clear as to how the anaesthetic agents interfere with the expression of withdrawal. One of the explanations is that anaesthetic agents can interfere with glutamate, which is associated with noradrenergic hyperactivity that partly underlies withdrawal signs.¹⁵

Important Terms

Detoxification: The removal or clearance of the intoxicating drug from the body.

Synonyms for anaesthesia-assisted detoxification³ (as used in the available literature) are rapid opiate detoxification, ultra-rapid opiate detoxification, anaesthesia-assisted opiate detoxification, rapid opiate detoxification under anaesthesia (RODA) and opioid antagonist detoxification under sedation or anaesthesia (OADUSA: preferred terminology of the American Society of Addiction Medicine).

One reason for the proliferation of terms is that the anaesthesia-assisted procedure was commercially used and was submitted as a registered trademark or patent. Therefore other researchers had to use other names to describe the procedure. Some authors have tried to differentiate between rapid detoxification and ultra-rapid detoxification according to the need for anaesthesia or heavy sedation. Procedures utilizing anaesthesia or heavy sedation while precipitating withdrawal are referred to as ultra-rapid opiate detoxification^{17,18} and those using opiate antagonist along with adjuvant medications without deep sedation or anaesthesia to accelerate withdrawal are termed as rapid opioid detoxification.^{2,19} What actually is being referred to as deep sedation or light sedation appears arbitrary. It appears that a host of terms are being used to refer to a group of loosely related procedures. Indeed, it has been recommended that the

terminology related to these procedures should be used more appropriately. Johnson and Carr²⁰ suggested classifying all the naltrexone-accelerated procedures as follows:

1. Ultra-rapid Opiate Detoxification (UROD): use of general anaesthesia; duration <6 hours.
2. Rapid Opiate Detoxification (ROD): deep sedation; duration 6-72 hours.
3. Compressed Opiate Detoxification (COD) and Naltrexone-compressed Opiate Detoxification (NCOD): duration between 3-6 days; also preceded by a period of abstinence from opioids under sedation prior to induction onto naltrexone.

Indications, Contraindications and Prerequisites for UROD

These may be grouped into patient-related and organisational factors.⁷

Patient-related factors

A highly selected subgroup of patients may benefit most from this procedure. This comprises patients who have been unable to abstain even with methadone substitution despite adequate motivation; those who are unable to stop methadone and continue with the last few milligrams of the same, and patients who are socially and occupationally active and cannot go through the usual long detoxification procedures without jeopardizing their jobs. Patients' preferences are also an important variable to consider. Its use should be restricted to patients with only opioid dependence as simultaneous dependence on other substances might complicate the procedure.¹² Certain contraindications and relative contraindications are as follows:²¹

Contraindications

- Pregnancy
- History of cardiac illness or evidence of the same on clinical examination
- Chronic renal impairment
- Decompensated liver disease
- Current dependence on benzodiazepines, alcohol or stimulants
- History of psychotic illness

Relative contraindications

- History of treatment for depression
- Unstable social circumstances. A comprehensive plan to stabilize such people should be undertaken prior to this procedure.

Organizational aspects

The procedure of rapid detoxification requires an intensive medical care unit (for administration of anaesthesia/deep sedation and monitoring), which should be preferably closely connected with the psychiatry or deaddiction unit to facilitate continuity of care. The team carrying out the procedure should have an anaesthetist, a specialist in intensive medicine, a psychiatrist, nursing staff and a psychotherapist/counsellor. This would ensure attention to the procedure, the immediate post-procedure complications as well as later abstinence-oriented programmes.²¹

Procedure of UROD

There are a host of programmes offering UROD, which differ in the exact procedure employed. However, following components/steps seem essential to any such programme:

1. Initial assessment, which involves obtaining a detailed history regarding the drug-intake and general medical and psychiatric illness.
2. Formulating a treatment plan and assessing the need for UROD.
3. Obtaining a written informed consent. The patient should be clearly and adequately informed of the available treatment options, the comparative costs incurred for each and the relative risks/advantages inherent in them.

Methodology

Pre-anaesthetic testing: The key issue is to identify the damage that the substance abuse might have caused. Apart from a detailed physical examination, recommended investigations are: haemogram; electrocardiogram; tests for excluding HIV, HBV and HCV; chest X-ray; liver and renal function tests.

Premedication: High-dose alpha-2 agonist blockade is introduced incrementally^{22,23} to reduce the systemic effects of withdrawal. Dexmedetomidine may be used intravenously as it is more selective, has a shorter duration of action and is easier to titrate than clonidine. Antiemetic medications (droperidol or ondansetron) are given simultaneously. Using buprenorphine for 1 week prior to UROD is believed to mitigate the intensity of the withdrawal syndrome.²⁴

Monitoring: Thorough anaesthetic monitoring of the vital functions is needed. Hensel et al²⁵ used EEG threshold monitoring to regulate the depth of anaesthesia with the advantage of being able to reduce the total dose of propofol, time to recovery from anaesthesia and objective withdrawal symptoms.

Induction and maintenance: Anaesthesia is induced with propofol or thiopentone.²⁶ Succinylcholine or mivacurium is used as muscle relaxant. Maintenance is done with an infusion containing a combination of midazolam²⁷ and propofol²⁸ or any inhalational agent on which the patient is not dependent. Most of the studies report the use of propofol, though methohexital^{29,30} has also been used. A test dose of the opioid antagonist is followed by an infusion of naloxone,^{7,23,31} naltrexone^{32,33} or nalmefene³¹ in normal saline via an orogastric tube into the stomach. Because a volume shift into the intestines is expected after administration of opiate antagonists, a liberal amount of ringer lactate is infused to maintain fluid balance.^{34,35} Thereafter, patients are monitored for withdrawal signs. The major sign of withdrawal under anaesthesia is piloerection as the other signs are masked by the use of alpha-2 agonist. Anaesthesia is maintained till the patients respond negatively to a dose of opioid antagonist. This is usually for 6-8 hours but may be longer in case of methadone-maintained patients.²⁵

Post-procedure monitoring and discharge: The usual policy is to discharge the patient within 24-36 hours. However, some patients who keep on complaining of persistent symptoms may be kept for a few additional days and managed symptomatically. A thorough check-up for any anaesthetic complications, withdrawal symptoms and psychiatric symptoms is recommended before discharge. Patients may stay in the inpatient psychiatric facility to initiate aftercare abstinence-oriented programmes.

Complications of UROD

There are only a few case reports available; hence, the actual prevalence cannot be worked out. Further, as the procedure has been commercialised, vested interests might hinder complete and accurate reporting of the complications. The following complications are anticipated and have been observed during the procedure:

- **Emesis and diarrhoea:**^{25,27} These are the prominent features of the withdrawal syndrome. Therefore antacids and antiemetics are used prophylactically. Ranitidine should be avoided as it may cause tachycardia, vomiting, insomnia and elevation of liver enzymes in higher doses. Diarrhoea should be treated with octreotide,³⁵ a synthetic polypeptide. It inhibits the anterior pituitary, suppressing the pancreas and thus inhibiting gastric acid, serotonin and VIP secretion which decreases gastrointestinal motility. Loperamide should be avoided as it is absorbed into systemic circulation and may increase the signs of withdrawal post-procedure.³
- **Sepsis:** Some centres also advocate the use of a single dose of an antibiotic, e.g. ceftriaxone to prevent infection.⁷
- **Gastric ulcer:** Presumably stress ulcer.³⁶
- **Vague neurological changes** (speech difficulties, peripheral numbness).
- **Idiosyncratic drug reactions.**³
- **Cardiovascular complications:** These include cardiovascular stimulation,³⁷ QT prolongation and bradycardia,³⁸ bigeminal cardiac arrhythmia,³⁹ partial subclavian vein thrombosis.²⁹
- **Renal failure:** Reported in occasional cases.^{34,40}
- **Suppression of thyroid hormones.**⁴⁰
- **Psychiatric complications:** these include dysphoria,³² psychotic episode requiring haloperidol,³⁹ suicide attempts on Day 3³⁹ and Day 5²⁷ post-procedure.
- **Deaths:** Deaths have been reported 16-40 hours following the procedure.⁴¹ In most of the cases the cause has been found to be pulmonary oedema, upper gastrointestinal ulceration and aspiration. One patient suffered from an intracerebral haemorrhage, presumably due to poor control of blood pressure.⁴² It was also seen that in these cases, the use of clonidine was a very restricted one and it was not continued after the procedure. In most of these cases, the routine/standards related to anaesthesia were also not followed.
- **Continuation of withdrawal symptoms:** Many patients continue to experience moderate withdrawal symptoms

after anaesthesia or sedation, including nausea, vomiting, diarrhoea, and sleep disturbances.^{43,44} Others report only mild to moderate symptoms only for the next 3-4 days.³¹ In addition, the severity of withdrawal may also be related to the anaesthetic used. However, without a controlled trial, no conclusion can be made regarding the duration or severity of withdrawal symptoms compared to other techniques of detoxification.

- **Complications related to intravenous naloxone:** Cardiac arrest and pulmonary oedema have been reported.⁴⁵

Effectiveness of UROD

Evaluation of the effectiveness of UROD would involve consideration of a variety of outcomes:

Number of patients enrolled: Many opioid-dependent patients may be fearful of prolonged detoxification programmes and thus may seek treatment only in an accelerated detoxification programme. This may itself be considered an important outcome.

Duration and severity of withdrawal symptoms: proponents suggest that the procedure is a rapid and painless method of detoxification. Therefore, an important outcome is the comparison of the duration and severity of withdrawal symptoms associated with ultra-rapid detoxification and other detoxification strategies.

Completion of detoxification: 30-91% of patients may drop out of traditional inpatient detoxification programmes. Using sedation or anaesthesia, one is assured of 100% completion of detoxification. It may be noted, however, that this 100% completion rate is by virtue of the method itself (because the patient is unconscious or deeply sedated and cannot physically run away till the basic procedure is over). Thus, the detoxification completion rate should not be used as an outcome measure in effectiveness evaluation of UROD.

Induction on to naltrexone: As expected, given the nature of the procedure, induction on to naltrexone is ensured in most of the procedures, although the actual data suggest otherwise (discussed later).

Period of abstinence: Rate of abstinence during both the short-term 6-month period of protracted withdrawal symptoms and longer-term abstinence are important outcome measures; indeed, one may argue that the *post-procedure* abstinence rate (short- or longer-term) constitutes one of the 'gold standards' for the effectiveness evaluation of UROD, provided the other therapeutic elements (naltrexone, psychosocial treatments, etc.) are comparable between the UROD group and the control groups. Few studies are available to suggest that UROD leads to a shorter or longer duration of abstinence.

Other measures of outcome might include patient satisfaction, programme evaluation and finally cost-benefit efficiency. It should be remembered that the patient populations treated are not similar. For example, patients dependent on heroin might respond differently than those dependent on crude opium and the response may vary according to the duration of dependence or prior attempts at traditional detoxification.

Available Evidence

In an extensive review of the literature, O'Connor and Kosten⁴⁸ studied the research design and methodological characteristics of 9 UROD and 12 ROD studies. These researchers noted that most of these studies used general anaesthesia except two, which used midazolam and propofol. Only three studies included a control group; only two studies used random allocation of patients and only one was blind. Most of the studies focussed on the completion of detoxification or severity of withdrawal symptoms over a duration ranging from 6 hours to 12 days. Only two studies evaluated outcome beyond the acute detoxification period. Legarda and Gossop²² reported that all the 11 subjects were still taking naltrexone after 30 days. Seoane et al⁴⁹ reported that 93% of the patients were abstinent after one month, although the methodology used to assess the same was not specified. They could not make a quantitative assessment of the effectiveness of UROD due to the variability of the patients and the techniques employed along with the small number of patients enrolled and suggested the need for more long-term studies on outcome including safety and efficacy.

Bell et al²¹ reviewed the literature from 1998-2000 and identified 21 studies on naltrexone-accelerated procedures. They concluded that the withdrawal syndrome was quite protracted in many of the studies as reflected in the duration of inpatient stay, which varied from 24 hours to 8 days with a mean duration of 3-4 days. Only 10 out of 21 studies reported on long-term outcomes. Five of these were concerned with detoxification under anaesthesia or deep sedation. The follow-up duration ranged from 3 months⁵⁰ to 1 year.²⁵ The abstinence rates ranged from 20% at 6 months²⁷ to 68% at 12 months.⁵⁰ One study compared relative abstinence rates in subjects undergoing UROD with those in a methadone-tapering group⁵⁰ and found it to be significantly higher (67%) in the former group as compared to 33% in the latter. In terms of induction onto naltrexone, all those who completed the UROD programmes were started on naltrexone.

In a retrospective follow-up study, Lawental⁵¹ compared subjects who had undergone UROD with those who had undergone a 30-day inpatient detoxification program (IDP) as adjudged by abstinence rates after 12 and 18 months. He found that only 22% in the former group reported abstinence as compared to 42% in the latter. He also commented on the cost-effectiveness of the alternatives to UROD. Krabbe et al⁵² compared abstinence rates and withdrawal effects of UROD with standard methadone tapering in a prospective 3-month follow-up trial. They found significantly higher abstinence rates and lesser and milder withdrawal symptoms in the subjects who had undergone UROD at 1 and 2 months follow-up duration. A similar trend continued at 3 months follow-up although the differences were no more significant. Tornay et al⁵³ followed up 16 patients over a period of 30 months after UROD and found that 14 of these relapsed.

The sample sizes of many of these trials are small, even many

recent trials (e.g., Krabbe et al⁵²) are not randomised, and patient and recruitment characteristics (e.g., whether or not they had to pay a fee for enrolment) might influence the results. Thus it would be premature to draw any firm conclusions from the presently available evidence on the efficacy of UROD.

UROD: The Controversy

It would be beneficial at this stage to review the potential benefits and disadvantages of this procedure.

Potential benefits:

The short-term effectiveness of this procedure is claimed to be 100%. Even if the claim regarding this '100% effectiveness' is contentious (see above), the fact remains that all the patients entering UROD therapy complete the detoxification process. A greater number of patients would enter long-term management protocols (usually with naltrexone maintenance and psychosocial treatments) and thus would at least have a chance to remain abstinent.

The procedure may be especially useful for a subset of patients who do not enter treatment for the fear of undergoing the painful conventional detoxification process. For the patients who are undergoing the process, it becomes more humane as they do not have to undergo the suffering and pain associated with the conventional detoxification procedures. According to a school of thought, it is one of the responsibilities of the physician to ensure minimal suffering and relief of pain.⁴ It may provide insights into the pharmacological modulation of withdrawal symptoms and their basis.

Potential harms/pitfalls:

The foremost is the risk of morbidity and mortality associated with the procedure, given the fact that there is practically none associated with the standard detoxification procedures. However, enthusiasts claim that if such a risk can be taken in other procedures associated with relief of pain, then the same should be justifiable in this too.⁵⁴ This issue assumes special relevance when consideration is given to the fact that there is always a possibility of under-reporting of complications related to the procedure due to vested financial interests.

The high cost of the procedure is another factor. The procedure requires an extensive set-up, close coordination between psychiatry and anaesthesia services and detailed monitoring post-procedure, which are not easily available.

There is no clear evidence that this procedure, as opposed to the standard detoxification, leads to greater abstinence rates. Although the immediate and short-term outcomes are encouraging, whether these can be considered as valid outcomes, in view of the nature of the procedure, is a debatable issue.

There are important ethical aspects to be considered: Some researchers have patented their versions of this procedure. The American Medical Association has taken a strong stand against these patents, calling them unethical.⁵⁵ From the point of view of patients, they may be extremely disturbed at the time of seeking treatment and hence vulnerable to exploitation by the sellers of a quick-fix to their problem. Further, there may be a selection bias operating at the treatment entry level itself,

which might spuriously influence the short-term results. The commercial providers often exploit this as a 'magic bullet', claiming excellent outcome as if that is a generalized truth applicable to *all* opioid-dependent patients. Other ethical concerns are: safety issues (see above), full disclosure to the patient regarding the procedure with its pros and cons, and providing the patient with a menu of viable options for treatment for which UROD is only one rather than the 'ultimate' choice. Such ethical concerns have been raised in the Indian scenario.⁵⁶

The American Society of Addiction Medicine (ASAM) has issued elaborate recommendations⁵⁷ for UROD incorporating many of the above ideas. It recommends that any method of opioid detoxification is only a first step, and is not in itself an effective treatment of opioid addiction.

Conclusion

Rapid/ultra-rapid detoxification attempts to answer the needs of opioid-dependent patients and expands the available treatment options. Although apparently useful in some contexts, the justification of this procedure lies in the resolution of the ethical conflicts surrounding the procedure and in methodologically sound long-term studies demonstrating greater efficacy over routine/standard detoxification procedures beyond the immediate detoxification period. Though rapid detoxification with the use of opioid-antagonists combined with alpha-2 adrenergic agonists is considered feasible, the anaesthesia-managed approach remains to be regarded as experimental.⁴⁵ Studies are also needed to understand the pharmacological basis of the procedure and further refine the use of medications during the procedure to minimize withdrawal symptoms and associated side-effects. In addition, guidelines need to be developed to guide practitioners and institutions in the use of this procedure to prevent any unethical practice related to the same and to maximise the benefit that patients can draw.

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