ISSN 1391-0736

The Sri Lanka Prescriber

December 2018; Volume 26, No. 4

1993 25 YEARS 2018

CELEBRATING THE 25TH ANNIVERSARY

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The Sri Lanka Prescriber

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Price per copy Rs 50.00 (students Rs 25.00). Personal callers may also obtain copies from the Departments of Pharmacology at the Medical Faculties in Colombo, Galle and Sri Jayewardenepura. The Sri Lanka Prescriber is available for downloading free of charge from the websites of State Pharmaceuticals Corporation (www.spc.lk) and Department of Pharmacology, Faculty of Medicine, University of Colombo (https://med.cmb.ac.lk)

Published by

Department of Pharmacology
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271, Kynsey Road, Colombo 8, Sri Lanka.
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Fax: + 94 11 447118
E-mail: prmanager@spc.lk Web site: www.spc.lk

Printed by

Ananda Press
82/5, Sir Ratnajothi Saravanamuttu Mawatha,
Colombo 13.
Telephone: + 94 11 2774793
E-mail: anandapress@ymail.com

Cover picture

SEPARATION OF PHARMACY AND MEDICINE (1240 A.D.)

Among world leaders who advanced Pharmacy's cause, none was more colorful than Frederick II, King of the Two Sicilies, who in 1240 by imperial edict granted Pharmacists independence from Medicine, and established legal responsibilities for each.

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The Sri Lanka Prescriber celebrates 25 years of publication

The Sri Lanka Prescriber which celebrates 25 years of continuous publication in 2018, is Sri Lanka's only national independent drugs and therapeutics information bulletin. It is published quarterly by the Department of Pharmacology, Faculty of Medicine, University of Colombo and the State Pharmaceutical Corporation (SPC) of Sri Lanka. The primary purpose of the bulletin is to help health professionals in Sri Lanka make informed decisions when prescribing, by providing them with independent and reliable information about drugs and therapeutics.

The Sri Lanka Prescriber commenced publication in the present format in 1993 and 2018 marks the 25th year of continued publication. *The Sri Lanka Prescriber* evolved from the pocket size bulletin, '*The Prescriber*' which began publishing in 1973 but went out of print in 1980's. Prior to that '*Formulary Notes*', was in existence from 1966 which was the first drug information bulletin published in Sri Lanka. *Formulary Notes* was also a pocket size bulletin, published on behalf of the Formulary Committee, initiated by Professor Senaka Bibile, the first Professor of Pharmacology, University of Ceylon and the Editor of *Formulary Notes*, to provide unbiased drug information to healthcare professionals. As the *Formulary Notes* had difficulties in publication, '*The Prescriber*' was launched in 1973 as a joint publication between the Formulary Committee and the State Pharmaceuticals Corporation (SPC), with funding and distribution managed by the SPC. *The Sri Lanka Prescriber* commenced as a joint publication by the Department of Pharmacology, Faculty of Medicine, University of Colombo and the SPC in 1993.

The Sri Lanka Prescriber became a full-member of the International Society of Drug Bulletins (ISDB) since 2001. In accordance with ISDB policy the Sri Lanka Prescriber does not accept advertising or other forms of sponsorship. This enables the bulletin to be wholly independent of the industry and other regulatory authorities, allowing it to publish freely and impartially on all matters related to medicines. The SPC bears the publication costs but does not influence contents of the bulletin, which are decided by the editorial board.

The print copy of The Sri Lanka Prescriber has a circulation of 7000, distributed free of charge to Sri Lankan healthcare professionals, including prescribing doctors, academics, researchers and students in universities, not only in medicine and dentistry but also in pharmacy. The bulletin has been made available online via websites of the SPC and the Department of Pharmacology Colombo since 2007.

For well over two decades, the bulletin has provided accurate, independent evaluations and practical advice on drugs and therapeutics for doctors, pharmacists and other healthcare professionals. The Editorial Board of the Sri Lanka Prescriber consists of experts from a variety of disciplines, including pharmacology, clinical medicine, paediatrics, gynaecology and obstetrics, psychiatry, anaesthesiology and dentistry. Surveys of our readership have consistently shown that readers find the bulletin influential in relation to their decisions, recommendations or advice on treatments, becoming an indispensable part of evidence based clinical practice in Sri Lanka. The Sri Lanka Prescriber is funded by the SPC of Sri Lanka as a service to the medical profession.

Editorial Board, The Sri Lanka Prescriber

Dry eye disease: when to treat and when to refer

Summary

Dry eye disease affects one in five adults, and can significantly impair quality of life. Most patients have mild disease.

This condition is multifactorial, with an inflammatory component which can markedly worsen the impact on the ocular surface. Meibomian gland dysfunction is extremely common in dry eye disease, and contributes to the inflammatory process.

Management of mild disease includes identifying and removing precipitants, and symptomatic treatment with artificial tear supplements.

More advanced disease requires management of underlying ophthalmic and systemic conditions, as well as more aggressive therapies to protect the ocular surface.

Keywords: aqueous deficiency dry eye, evaporative dry eye, meibomian gland dysfunction

*(Aust Prescr 2018; **41**: 160-3)*

Introduction

Dry eye disease, or keratoconjunctivitis sicca, is highly prevalent, and can have significant adverse effects on quality of life. It is 'a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film, and accompanied by ocular symptoms in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play aetiological roles'.[1]

As a leading cause of patient visits to both optometrists and ophthalmologists, it is a substantial burden on the healthcare system. While most patients have mild disease and need only simple treatment, complex interventions in severe disease aim to prevent progression to corneal ulceration and conjunctival scarring. It should be noted that dry eye disease is worsened by contact lens wear and refractive laser surgery.

Dry eye disease subtypes

There are two main subtypes of dry eye disease – aqueous deficiency and evaporative. These may co-exist.[2]

Aqueous deficiency

Aqueous deficiency occurs because of reduced aqueous production from the lacrimal glands. It accounts for only a tenth of dry eye disease. Aqueous deficiency can be further separated into Sjögren's syndrome-related and non-Sjögren's syndrome related.

Evaporative

Evaporative dry eye is due to a deficient tear film lipid layer, which increases tear evaporation. It is caused by meibomian gland dysfunction, which occurs in over 85% of dry eye disease. Blepharitis, or lid margin inflammation, is both a cause and an effect of meibomian gland dysfunction. The differential diagnosis of blepharitis includes ocular rosacea and atopy, seborrhoeic dermatitis, staphylococcal infection and *Demodex* mite infestation. Tear deficiency is thought to alter resistance to infection, so dry eye disease is both a cause and an effect of blepharitis.

Risk factors

Multiple factors contribute to the development of dry eye disease (Box 1). Female gender is the most consistently identified risk factor, with the prevalence in women being almost double that in men. Advancing age is also a major risk factor, possibly due to decreased androgen levels, since androgen up-regulates meibomian gland function in animal models. While oestrogen is thought to down-regulate it, there is uncertainty as to whether hormone replacement therapy exacerbates or improves dry eye disease.[3]

Diagnosis and assessment

Accurately diagnosing dry eye disease and determining its severity is confounded by the variability in clinical presentation. Patients often report non-specific symptoms, such as visual disturbance, photophobia and ocular discomfort, including foreign body sensation, grittiness and burning. Paradoxically there may be excessive wateriness, as discomfort triggers reflex tearing. The severity of symptoms does not correlate well with the severity of signs seen at the slit lamp, especially if there is a low pain threshold (symptoms exceed signs), or if there is reduced corneal sensation (signs exceed symptoms).

All of these symptoms may be present in other unrelated eye conditions such as ocular allergy, corneal erosion and foreign body. Differential diagnoses must be considered

when symptoms are severe or unilateral. Box 2 outlines when referral for specialist assessment is needed.[4]

Dry eye questionnaires such as DEQ-5 or OSDI have been developed and validated for screening and/or measuring severity and response to treatment. However, they are not in common use. Clinical assessment and various tests are required to diagnose dry eye disease.

Ocular surface staining

In dry eye disease, there is loss of the protective glycocalyx barrier, due to increased shedding of the corneal and conjunctival epithelial cells.[5] The new underlying cells are able to absorb vital dyes, with the degree of pathological staining matching disease severity. Areas of epithelial cell loss are readily seen using sodium fluorescein drops under cobalt blue light at the slit lamp.

Tear film break-up time

Tear film break-up time is reduced in dry eye disease. Again using sodium fluorescein drops under cobalt blue light at the slit lamp, the time it takes for the first dark spot to appear in the fluorescein-stained tear film since the last complete blink is measured. A tear break-up time less than 10 seconds indicates tear film instability, and a measurement less than five seconds diagnoses dry eye disease.

Tear lake

The tear meniscus seen at the inferior lid margin is reduced in dry eye disease. Less than 0.2 mm is diagnostic.

Blepharitis

Debris is seen on the lashes and there may be reddening, telangiectasia and thickening of the lid margins.

Meibomian gland assessment

Objective meibomian gland assessment is important for diagnosing evaporative dry eye disease. Healthy meibomian glands should discharge a transparent liquid oil under gentle pressure to the lid margin, whereas thick or discoloured meibum indicates gland dysfunction. 'Pouting'of the gland orifices at the lid margin may be seen due to retained meibum.

Schirmer's test

Schirmer's test is used to diagnose aqueous deficiency dry eye disease. It is more invasive than the tests above, as a Schirmer strip composed of filter paper is placed into the lower fornix for five minutes. Anaesthetic drops are instilled first, to prevent reflex tearing due to irritation by the paper. A measurement less than 5 mm is consistent with low aqueous tear production.

Box 1 **Causes and risk factors for dry eye disease**

- Female gender and advancing age, possibly hormone replacement therapy
- Blepharitis/meibomian gland disease – rosacea, seborrhoeic dermatitis, staphylococcal infection, *Demodex* mite infestation
- Lagophthalmos – facial nerve palsy, proptosis, vertical lid shortening
- Decreased blinking – prolonged computer use or other visual task, Parkinson's disease
- Ocular autoimmune disease – atopy, cicatricial pemphigoid
- Systemic autoimmune disease – Sjögren's syndrome, lupus, scleroderma, chronic graft-versus-host disease, rheumatoid arthritis
- Other medical causes – vitamin A deficiency, hepatitis C, thyroid disorders
- Antihypertensives, antihistamines and antidepressants
- Exogenous factors – radiation therapy, chemical injuries
- Low-humidity environments e.g. air conditioning or heating
- Low intake of omega-3 fatty acids

Box 2 **NICE guidelines for referral to an optometrist or ophthalmologist**

- Patients with moderate-severe eye pain, photophobia, marked redness in one eye or reduced visual acuity (same day referral)
- Deteriorating vision
- Ulcers or signs of corneal damage
- Persisting or worsening symptoms despite appropriate treatment for four weeks
- Associated disease requiring specialist treatment e.g. Sjögren's syndrome, eyelid deformities

Source: reference 4

Other tests

Tears can also be analysed for hyperosmolarity, and for the cytokine MMP-9 as a marker of inflammation and dryness.[6]

Management

Treatment of dry eye disease aims to relieve symptoms, and to reduce any risk of ocular surface damage. Tear film homeostasis should be restored as much as possible.

Box 3 **First-line treatments for mild dry eye disease**

- Apply ocular lubricants – drop, gel or ointment depending on severity of symptoms, preferably unpreserved. Consider adding a lipid layer stabiliser.
- Treat blepharitis – lid wipes, rosacea management, eradication of infection e.g. oneweek course of chloramphenicol ointment to lid margins.
- Optimise meibomian gland function – warm compresses, warming eye masks.
- Modify the environment to decrease evaporation of tears – increase air humidity, reduce computer use, increase frequency of breaks for eye rest, 'conscious blinking'.
- Review drugs that may exacerbate eye symptoms e.g. antihistamines, beta blockers, tricyclic antidepressants, selective serotonin reuptake inhibitors, isotretinoin, eye drops with preservatives.

Mild disease

Box 3 provides a summary of first-line treatments for mild dry eye disease. Many of the treatments for mild symptoms are available from the pharmacy (Table).

Lubricants

Artificial tear drops to supplement the aqueous component of the tear film are the first-line therapy for patients with mild symptoms. For moderate symptoms, gels are used during the day. Lubricating ointment is only applied at night, as it causes blurring of vision. The regular use of artificial tears, gels and ointment increases tear film break-up time, and reduces signs of corneal damage – a month's treatment produces improvement of around 25%.[7] An insert retained by the lower lid (Lacrisert) provides a slow-release alternative to conventional lubricants. Newer preparations seek to stabilise the lipid layer of the tear film, and can be used in conjunction with lubricants augmenting the aqueous layer.

Preservatives

Preservatives such as benzalkonium chloride are commonly found in eye drops, including artificial tears, corticosteroids, antibiotics and glaucoma medicines. These can cause irritation and exacerbate dry eye disease. However, because preservatives are diluted in the tear film, they remain suitable for patients with mild dry eye. In more severe disease, the dilution effect is attenuated due to

Table **Examples of pharmacy treatments for dry eye disease**

Main lubricant	Presentation	Preserved
'Aqueous' tear supplements		
Carmellose sodium (Cellufresh, Celluvisc)	Single-use vial	No
Polyethylene glycol or propylene glycol (Systane drops or gel drops)	Single-use vial Multi-dose bottle	No Yes
Sodium hyaluronate (Hylo-Fresh, Hylo-Forte)	Multi-dose bottle	No
Carbomer (Poly Gel)	Single-use vial	No
Carboxymethylcellulose sodium, hypromellose (Genteal gel)	Multi-dose tube	Yes
'Lipid' tear supplements		
Propylene glycol, emulsified mineral oil (Systane Balance)	Multi-dose bottle	Yes
Soya lecithin (Optrex ActiMist) closed lids)	Multi-dose spray Yes	
Perfluorohexyloctane (NovaTears)	Multi-dose bottle	No
Lid cleansers		
Foam solution containing plant oils (Sterilid)	Pump bottle	No
Lid wipes (Systane)	Wipes	No

reduced tear volume, so preservative-free eye drops are recommended.

Meibomian gland dysfunction

Every effort must be made to treat blepharitis and meibomian gland dysfunction. Strategies include using lid wipes or foam cleansers, doxycycline for ocular rosacea, warm compresses or eye masks, and expression of blocked glands.

Extrapolating from its use in facial rosacea, some optometrists and ophthalmologists now offer intense pulsed light therapy to improve meibomian gland function. Treatment is applied across the zygomatic arches, lower lids and bridge of the nose, while the patient is wearing opaque goggles. A variety of treatment mechanisms are proposed,[8] but there are limited studies to date. A thermal/pulsation system (LipiFlow) provides an automated method of lid margin heating and massage, and is also aimed at improving meibomian gland function.

Refractory disease

Certain patient populations have more refractory disease and require more aggressive intervention to reduce the risk of permanent ocular surface injury. This includes patients with rheumatoid arthritis or Sjögren's syndrome, and those with cicatrising disease of the conjunctiva, such as severe atopy or ocular pemphigoid. Here the foundation of care is optimal treatment of the underlying systemic disease, with co-management of the patient by both an ophthalmologist and an immunologist or rheumatologist.

Medical treatments

Topical anti-inflammatory drugs are used by ophthalmologists for more severe cases. However, topical corticosteroids are sparingly prescribed, due to the risk of glaucoma, infection and keratolysis.

Immunomodulatory drugs with anti-inflammatory effects such as ciclosporin eye drops (0.05-0.1%) have been shown to reduce symptoms and corneal surface damage.[9] Tacrolimus eye drops (0.02-0.03%) are a viable alternative for patients who are unable to use ciclosporin, or do not benefit from it.[10] Testosterone eye drops (0.03%) have shown promise in very limited settings,[11] but like tacrolimus can only be obtained from a compounding chemist.

Autologous serum eye drops, containing growth factors, vitamin A and fibronectin, are effective in severe dry eye disease. However preparation is laborious, and the procedure is only available in hospitals.[12]

Surgical treatments

Reduction of tear drainage by punctal occlusion, with dissolvable or permanent plugs, has been shown to provide symptomatic improvement, particularly in aqueous deficiency dry eye disease and when combined with other treatments. Permanent surgical closure is offered if clinical benefit is obtained from temporary plugs.

Severe lagophthalmos may need to be addressed with botulinum toxin-induced ptosis if temporary, or tarsorrhaphy if permanent.

Referring appropriately

GPs and pharmacists are well placed to recommend the interventions in Box 3 for mild disease. For more severe symptoms it is appropriate to refer a patient to an optometrist before an ophthalmologist. An optometrist can perform a specialised eye examination, including a comprehensive dry eye disease evaluation, using equipment that is not normally available in general practice. The National Institute for Health and Care Excellence provides concise recommendations on when to refer patients (Box 2).[4]

Conclusion

Dry eye disease is common, and particularly prevalent in older women. Management of mild disease consists of tear supplements from the pharmacy as first-line treatment, and techniques to manage meibomian gland dysfunction. Patients with more severe symptoms or risk factors for ocular surface damage can be assessed by an optometrist, then referred to an ophthalmologist as needed for more advanced interventions.

Conflict of interest: none declared

Acknowledgement: The authors would like to thank Dr Laura Downie for her assistance in editing this review.

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Further reading

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Management of pain in an adult patient at the end of life

Introduction

Pain is a main concern identified by the general public and doctors regarding fears at the end of life and death. They have a fear that pain cannot be controlled effectively without unpleasant side-effects.

The need for end of life care is expected to rise sharply in the next 15 years. Controlling pain is a major concern in specialist palliative care. The concept of palliative care has been broadened from cancer to all advanced life threatening illnesses.

A greater focus has been directed by experts in pain medicine towards supporting improvements in palliative care, in particular the use of stronger analgesics such as opioids. Opioids are the mainstay of pain management in patients at the end of life, and other analgesics have to be combined with opioids to improve pain relief. It has become difficult to decide therapy in non-cancer pain as the available data and experience in management of pain is limited.

Guidelines for pain relief

One of the most commonly used guidelines employed in provision of pain relief is the WHO Analgesic Ladder (WHO-AL) (Figure 1)

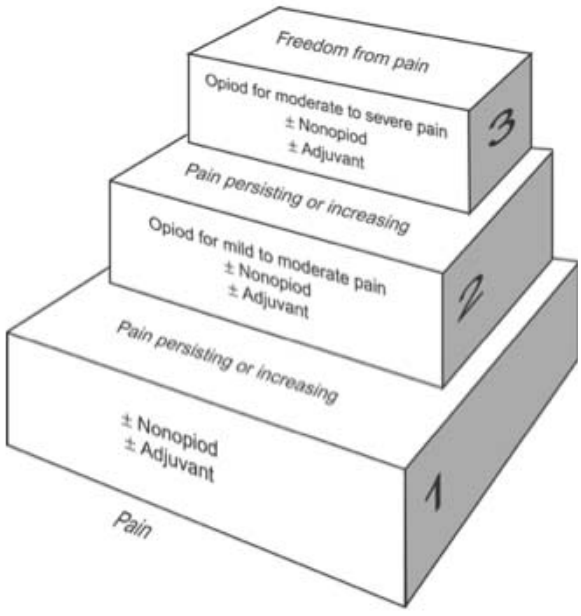

Figure 1. WHO Analgesic Ladder (WHO-AL)

It is estimated that 70-90% of the patients have adequate pain relief when appropriate drugs and dosages are prescribed as shown in the WHO-AL.

For finding the appropriate drug and the dose, assessment of pain plays a pivotal role. Degree of pain can be assessed by using a suitable pain measuring tool (eg. numerical scale) for deciding the dose. Type of pain assessed by taking a good history of the nature of pain will be a useful guide for selecting the most appropriate medication.

Table 1. Principles of using WHO-AL in pain therapy

Analgesics should
1. be given by the clock (ie. at regular intervals)
2. by mouth preferably
3. tailor the dose (according to the degree of pain)
4. treat 'breakthrough pain'
5 use co-analgesics when necessary

If one drug on a particular step does not provide adequate pain relief with the appropriate dose, move up on a step rather than trying another drug of the same step

Step 1 – WHO-AL

- Is indicated for mild pain
- A non-opioid in this step is paracetamol (15mg/kg per dose 6 hourly)
- An alternative to paracetamol is a non-steroidal anti-inflammatory drugs (NSAIDs).
- NSAIDs are indicated for bone pain.
- Two NSAIDs should not be given simultaneously.
- A proton pump inhibitor once daily ½ hour before breakfast with a glass of water is recommended.

Step 2 – WHO-AL

- Is indicated for mild to moderate pain.
- Add a step 2 drug (eg. codeine) to the regular drug from step 1.
- Compound paracetamol-codeine preparations are unlikely to be effective as the amount of codeine is too little.
- Recommended codeine dose is 30-60 mg every 4 hours up to a maximum of 240 mg/day.
- Codeine has a ceiling analgesic dose of 240 mg/day. Hence there is no great benefit in taking codeine 60 mg 4 hourly.

- Codeine is metabolized in the liver by the enzyme CYP2D6 into morphine.
- Ten percent of the general population who do not have this enzyme responds poorly to codeine. An alternative to codeine is dihydrocodeine controlled release 120 mg two times a day.
- If pain is not controlled with codeine, do not switch to dihydrocodeine but move to Step 3.
- Tramadol has an opioid-like action and increases serotonin and noradrenaline in the inhibitory pain pathway. Effective in moderate to severe pain but can cause troublesome nausea, drowsiness and occasionally CNS excitation.

Step 3 – WHO-AL

- Morphine is the first choice for moderate to severe pain.
- Morphine is combined with non-opioid used in Step 2

Administration of morphine

- Start morphine orally – either morphine elixir or immediate release morphine (Morphine IR)
- Effective pain control can be achieved by giving regular oral Morphine IR, 4 hourly
- For an adult who is on Step 2 drugs with a regular weak opioid, an appropriate starting dose is oral Morphine IR is 5 mg, 4 hourly
- For an adult who is not currently on a weak opioid, the dose is usually reduced to 2.5-5mg 4 hourly
- In the elderly or patients with renal impairment start with 2.5 mg 4 hourly
- Maintaining a written record (eg. in a diary) of rescue doses for the treatment of breakthrough and incident pain is important.

Breakthrough pain

Is the pain which breaks through the basal level of analgesia.

This can occur

1. during dose titration or
2. when pain is normally controlled by Morphine SR (slow release)

In both situations, rescue dose is given as Morphine IR as $1/6^{th}$ of total daily dose of morphine

If doses of Morphine IR are needed consistently as rescue doses ($\geq$ two times per day), they are incorporated into Morphine SR twice daily dose.

Incident pain

This is pain on movement or activity. Doses of Morphine IR can be given when the aggravating event occurs or before an activity that is known to bring on pain.

When Morphine IR is given regularly for this type of pain, there is a high risk of adverse effects. Doses for incident pain are not added to the total daily dose of Morphine SR. If pain relief is not adequate due to inadequate basal dose, 4 hour dose (Morphine IR) is increased by 35-50% and pain is re-assessed.

Once the pain is controlled over 24 hours Morphine IR can be switched onto Morphine slow release (Morphine SR). Morphine SR is given 12 hourly. Dose is equivalent to half of the total daily dose of Morphine IR. If the patient cannot take orally, morphine is administered as a subcutaneous (SC) infusion with a syringe drive. SC daily dose is equivalent to 50% of Morphine IR daily dose.

Management of adverse effects of morphine

Monitoring of adverse effects is important for early detection and treatment. Nausea and vomiting are not commonly seen in cancer patients on morphine, whereas constipation is quite common.

1. Constipation. Provide a laxative and review regularly. Start the laxative at the same time with initiation of morphine therapy. This will reduce the problem of stool impaction. A combination of a stimulant and a stool softener is recommended.
2. Drowsiness. Minimal in patients with stable doses of morphine. Patients just starting or who just had an increase of the dose may develop drowsiness.
3. Nausea and vomiting. Commonly occurs at the commencement of the treatment. However these symptoms are transient. A search to find a cause for vomiting should be made (eg. drug induced, gastric stasis or a pathological cause).

   Suitable antiemetic drugs and doses

   Haloperidol 0.5-1.5 mg in the night is the first choice.

   Metoclopramide. Indicated when gastric stasis is present. Start with 10 mg 3 to 4 times a day. Avoid in bowel obstruction. Used for short term treatment of less than 2 weeks.

   Cyclizine. 25-50 mg 8 hourly, useful if symptoms are aggravated by movement or central in origin (eg. brain tumour).
4. Respiratory depression. Diagnosed when respiratory rate is < 8 per minute. This rate is unlikely unless a very high dose has been given. Management includes giving oxygen via face mask, stopping morphine until respiratory rate rises, and naloxone given intra-venously.

If naloxone is titrated to respiratory rate and level of consciousness with small aliquots (20 micrograms), an acute pain crisis may not occur. When re-starting morphine, consider a reduced dose.

Opioid toxicity

Toxicity occurs when

- doses are increased too rapidly
- renal impairment is present
- high doses are used in spite of having a poor response to increasing doses of morphine
- An adjuvant pain relieving interventions have been given for pain relief but baseline drugs not reduced

Table 2. Signs of morphine toxicity

- Pin-point pupils
- Hallucinations
- Drowsiness
- Confusion
- Vomiting
- Respiratory depression
- Myoclonic jerks

Management of toxicity.

1. Opioid should be stopped.
2. Hydrate the patient adequately.
3. Delirium may be treated with haloperidol when toxicity subsides.
4. Once toxicity is controlled opioid can be started at a lower dose, or alternative opioid can be given at a lower equivalent dose.

The need for increased doses of morphine for pain relief is usually related to a change in the disease process rather than addiction. There is no clinical need to consider dependence at the end of life care.

Alternative strong opioids

Alternative opioids are indicated in

- morphine intolerance
- severe renal impairment
- difficulties with poor oral intake
- poor analgesic response

Alternative strong opioids are methadone, oxycodone, hydromorphone and fentanyl.

If a switch from morphine to another opioid is needed, admission to the hospital is indicated. There is only limited evidence for the effectiveness of switching to another opioid in the management of cancer pain.

Methadone has a long half-life, complex and variable pharmacokinetics and can accumulate on repeated injections. Is a safer alternative in renal failure. It is usually administered under specialist guidance.

Oxycodone. Available in two forms, controlled release (Oxycontin) and immediate release (Oxynorm). Oxycodone has high oral bioavailability. It is 1.5 to 2 times as potent as oral morphine. It can be used without toxic effects in patients with renal failure. Patients who are being switched from oral morphine should initially get half the dose of oral oxycodone.

Hydromorphone. Available in short and long acting forms. It is metabolized in the liver and excreted by the kidneys. It is safer than morphine in renal impairment. It can be given subcutaneously.

Fentanyl. Is available as a transdermal patch and this allows controlled release over 72 hours. Morphine can be switched to fentanyl if intolerable side-effects develop or if patient is unable to take orally. The onset of action is 12 to 24 hours, so patients require another strong opioid for breakthrough pain while switching. It should only be used in patients with stable opioid requirement. The duration of action of the patch is approximately 72 hours and residual effects can be noted for about 12 to 24 hours after removal of the patch. Fentanyl 50 microgram/hour patch is equivalent to 120 mg morphine (oral) per day. The dose is too strong perhaps for an opioid naïve patient and may lead to opioid toxicity.

Note: Pethidine is not used in palliative care.

Adjuvant therapy for neuropathic pain (NP)

Treatment of NP is only described here as it is a major component of pathological pain.
It is commonly treated with

1. Tricyclic antidepressants (TCA)
2. Anti-epileptic drugs

However, there is no significant difference identified between these two groups in effectiveness or overall incidence of adverse effects.

Tricyclic antidepressants (TCAs)

- Are better tolerated than antiepileptics.
- Effective at lower dose, but may aggravate opioid induced constipation.
- Nortriptyline is preferred to amitriptyline as it has fewer anti-cholinergic effects and causes less postural hypotension.

- TCAs and antiepileptics can be used in combination but additive effects may occur and may increase drowsiness.

Suggested doses.

1. Nortriptyline – 10-50 mg at night.
2. Amitriptyline – 10 mg at night, the starting dose may increase to 75mg.
3. Sodium valproate – start with 200 mg twice daily and titrate according to the response. Usual maintenance dose is 400-1200 mg/day, in divided doses.
4. Carbamazepine – start with 100 mg daily and titrate by 100 to 200 mg every 2 weeks. Usual maintenance dose is 200 mg 3 to 4 times a day. Carbamazepine has many drug interactions and toxicity can be increased by concurrent therapy with drugs that inhibit CYP3A4 enzyme.
5. Clonazepam – 0.5-2mg at night. Titrate the dose slowly. May cause drowsiness and ataxia. There is little evidence to support effectiveness.
6. Gabapentin – Start with 300 mg in divided doses and titrate up to a maximum dose of 2400 mg per day. In most patients the effective dose is 900 to 1800 mg per day.
7. Pregabalin – Start with 75 mg twice daily and increase gradually to 150 mg twice daily according to the response. It may take weeks to achieve maximal effect. Do not discontinue abruptly.

Corticosteroids in cancer pain

They reduce oedema and inflammation and pressure associated with tumours.

The evidence for actual doses of steroids is meagre, and mostly doses are dependent or local practice and opinion.

- Document the indications and plan clearly when steroids are first administered.
- They can be down-titrated while symptom control is maintained.

Indications for use of corticosteroids

1. Neurological – Increased intracranial pressure, spinal cord compression and nerve compression or infiltration.
2. Capsular stretch – Liver metastasis or other visceral metastases.
3. Soft tissue infiltration – Head and neck tumours, abdominal and pelvic invasive tumours.
4. Tenesmus.
5. General wellbeing – Appetite stimulation and anti-emetic.

Authorities emphasise that there is little evidence to suggest that appropriate use of analgesics in control of pain hastens death or causes respiratory depression.

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Conflicts of interest: none declared

Management of stroke: An overview

Introduction

Stroke is a leading cause of death and disability. One in every hundred living in Colombo and its suburbs are affected by stroke [1]. Stroke is broadly classified into ischaemic and haemorrhagic stroke. Ischaemic stroke accounts for 87%, and is defined as an "acute focal neurological dysfunction caused by acute focal infarction at single or multiple sites of the brain or retina". Haemorrhagic stroke (intracerebral haemorrhage or ICH) is defined as "acute neurological dysfunction caused by haemorrhage within the brain parenchyma or ventricular system". Subarachnoid haemorrhage (SAH), transient ischaemic attacks (TIA), and silent cerebrovascular disease are other important related entities that are not discussed in this article.

Diagnosis of stroke is based on history, clinical features, imaging and by exclusion of stroke mimics. It is important to establish a causative mechanism for specific management and secondary prevention. Treatment of acute stroke is a time dependent medical emergency. Knowledge and basic skills on diagnosis of stroke among the public is pertinent to improve advanced time-based forms of treatment available in many leading hospitals in Sri Lanka.

Risk factors

There are well established risk factors for development of stroke (Table 1). Presence of multiple risk factors tends to increase the risk of development of stroke. Hypertension is by far the most important modifiable risk factor. Whilst risk prediction charts developed using data derived from a particular community assist in predicting total risk of developing cardio-vascular disease for the people in that community, intervening factors at individual and community level significantly reduces the risk of developing CVD including stroke. Studies suggest that 90% of strokes are caused by modifiable risk factors and 80% of recurrent stroke could be prevented by optimal risk factor control.

Aetiology

Stroke is a heterogenous disease with a many causes. Aetiology invariably originates either from a blood vessel wall, heart or from blood constituents. Trial of Org 10172 in Acute Stroke Treatment (TOAST) classifies stroke based on aetiology (Table 2). Once investigations are completed, 25-39% are labelled as stroke of undetermined aetiology or cryptogenic stroke.

Table 1. Risk factors for development of stroke

Non- Modifiable	*Modifiable*	
	Lifestyle related	*Disease related*
Old age	Smoking	Hypertension
Male gender	Alcohol	Diabetes mellitus
Positive family history	Unhealthy diet	Hyperlipidaemia
	Lack of exercise	Heart disease
	Oral contraceptive pills	Obesity

Table 2. Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification based on aetiology

Large artery atherosclerosis	>50% stenosis of major intra- or extra-cranial artery causing infarction > 1.5cm
Cardioembolism	High risk or medium risk cardiac lesion causing cardioembolism
Small vessel disease	Clinical lacunar syndrome without evidence of cortical dysfunction with normal or subcortical infarction <1.5cm in brain imaging
Stroke of other determined cause	Antiphospholipid syndrome, vasculitis, hypercoagulable state, haematological disorders, etc.
Stroke of undetermined cause	Negative diagnostic studies, incomplete evaluation or two or more conflicting causes

Clinical features

The clinical features of stroke are determined by the anatomical location of the cerebral pathology. Hemiparesis and speech disturbance are the most common symptoms that occur in 90% of patients. Hemianesthesia, vision disturbance, dysphagia, incoordination, sphincter dysfunction, ataxia and loss of consciousness are less common symptoms. The use of abbreviation "FAST'' indicating involvement of Face, Arm and Speech (T for time) for rapid diagnosis of stroke by laypersons is relevant and highly reliable. While arriving at the clinical diagnosis based on sudden onset of clinical features, exclusion of stroke mimics such as hypoglycemia, seizures with post-ictal paralysis, tumours, cerebral abscess, psychogenic weakness and hemiplegic migraine are essential for management.

Oxfordshire community stroke project (OCSP) classification classifies ischaemic stroke, based on clinical features and CT changes, into total anterior circulation infarctions (TACI), partial anterior circulation infarctions (PACI), posterior circulation infarctions (POCI) and lacunar infarctions (LACI). OCSP classification is useful for management decisions and for prognostication. As aetiology is not revealed in OCSP, upon completing investigations, further classification based on TOAST (Table 2) is warranted.

Imaging

Clinical diagnosis of stroke should be immediately followed by the pathological diagnosis, ischaemic vs haemorrhagic stroke. Non-contrast cranial CT shows changes of cerebral haemorrhage from the time of onset of clinical features but takes hours for appearance of infarctions. It is freely available, less costly and interpretation is straightforward. While MRI brain has many advantages, it is less available, more expensive, more time consuming and requires expertise for interpretation. Both techniques provide angiogram facilities and are complementary for advanced evaluation.

Acute management of ischaemic stroke

Hospitals practising acute management of stroke with thrombolysis should have trained staff and protocols for management in place at the emergency treatment unit (ETU) and radiology unit to ensure minimum delay in administering thrombolytic agent. Recombinant tissue plasminogen activator (rtPA) was introduced for management of acute ischaemic stroke in 1995 following the national institute of neurological disorders and stroke (NINDS) trial [2]. Since then, the criteria have been revised to include more patients to enjoy benefits of treatment (Table 3).

Once stabilized in ETU, National Institute of Health (NIH) stroke scale/score documented eligibility for thrombolysis with recombinant tissue plasminogen activator (rtPA, alteplase), and imaging of brain (Table 3). When given within 4.5 hours from onset of ischemic stroke to eligible patients, alteplase has been shown in randomized controlled trials to decrease functional disability with an absolute risk reduction of 7-13% relative to placebo [2, 3]. Treatment efficacy wanes rapidly, and risk of cerebral haemorrhage that occurs in 6-8% increases with time that elapses from onset of symptoms. Once all eligibility and exclusion criteria are fulfilled for thrombolysis, having explained the patient or guardian the risk involved with thrombolysis and consent is obtained, patient should receive alteplace 0.9 mg/kg body weight intravenously with a maximum dose of 90 mg per individual. Ten percent of the dose is given as a bolus over 1 minute and the rest as an infusion over one hour. Patient should be monitored preferably in an ICU setting for the next 24 hours. NIH stroke scale/score and blood pressure measurements should be checked every 15 minutes for the first 2 hours, every 30 minutes for the next 6 hours, and hourly for next 16 hours. Blood pressure should be maintained less than 180/105 mmHg by infusing intravenous labetalol if required, within the next 24 hours post-thrombolytic period. If neurologic deterioration occurs, alteplase should be discontinued and a CT brain obtained. At the end of 24 hours a repeat CT is obtained and once haemorrhage is excluded antiplatelets or anticoagulants that are required for secondary prevention could be commenced.

According to the NINDS trial, although there was 12% absolute increase in favourable outcome with rtPA given within 3 hours, there was a 6% increase in symptomatic haemorrhage. Strict adhering to protocol is recommended as haemorrhages are commoner with protocol violations. Risk for ICH was higher with elevated glucose, high NIH stroke scale/score, advanced age, elevated blood pressure, thrombocytopenia, congestive heart failure, CT changes of infarction and delayed thrombolysis. Symptomatic ICH following rtPA are generally large and carries a poor prognosis. Whilst there are no evidence based recommendations for management, it is sensible then to discontinuing rtPA, and to treat with 6-8 units of platelets and 10 units of cryoprecipitate for symptomatic patients.

Poor reperfusion following rtPA in large vessel occlusions and cardioembolism is a major limitation of intravenous thrombolysis. Current evidence supports thrombectomies for angiogram proven internal carotid occlusion and for M1 segment occlusion of the middle cerebral artery within the first 6 hours [4]. Therapeutic window of treatment with thrombectomies could be further widened to 24 hours with advanced MRI techniques with diffusion perfusion scans which establish existence of viable cerebral tissue as ischaemic penumbra. Therefore, CT angiogram should follow the cranial CT in all patients, to study the vascular tree. In a setting where interventional facilities are available, while thrombolysis with rtPA is carried out, eligible patient should undergo thrombectomy. Thrombectomy should not delay thrombolysis with rtPA by any means.

Table 3. Acute Stroke Care Programme (ASCaP) – NHSL, Colombo

Thrombolysis check list

Inclusion criteria	**Yes**	**No**
1. Diagnosis of ischaemic stroke with measurable neurological deficit (Defined as impairment of language, motor function, cognition, gaze, vision or neglect)		
2. Symptom onset within 0-4.5 hours		
3. Age ≥ 18 years		

Absolute contraindications

1. Past history of intracranial haemorrhage, arteriovenous malformations (AVM)	
2. Subarachnoid haemorrhage suspected even with normal CT	
3. Intracranial neoplasms (intra-axial)	
4. Intracranial or spinal surgery within the prior 3 months	
5. Major surgery or serious trauma within 14 days	
6. Serious head trauma within 3 months	
7. Patients with a structural gastrointestinal malignancy or recent bleeding event within 21 days	
8. Arterial puncture at a non-compressible site within 7 days	
9. INR >1.7	
10. APTT > 40 seconds	
11. Platelet count <100 000/cmm	
12. Heparin within last 48 hours with elevated APTT	
13. Patients receiving low molecular weight heparin (LMWH) within 24 hours*	
14. Direct thrombin inhibitor or factor Xa inhibitor within 48 hours*	
15. Non-contrast CT showing hypodensity > 1/3 of the cerebral hemisphere	

* laboratory tests such as APTT, INR, ecarin clotting time, thrombin time, or direct factor Xa activity assays are normal

Relative contraindications	**Yes**	**No**
1. Rapidly improving symptoms		
2. Aneurysms unruptured and unsecured aneurysm <10mm		
3. Ischaemic stroke within 3 months		
4. Acute anterior myocardial infarction within last 3 months		
5. Major extracranial trauma within 14 days		
6. Seizure at onset with post-ictal residual neurological impairments		
7. Systolic blood pressure >185 mmHg or diastolic blood pressure >110 mmHg (treatment recommended if blood pressure can be lowered safely)		
8. Pregnancy		
9. Blood glucose < 50mg/dl and > 400mg/dl subsequently normalized (Treatment recommended if neurological deficits persists after correction)		
10. Intracranial neoplasms (extra axial)		
11. Gastrointestinal or urinary tract haemorrhage within 21 days		
12. Minor stroke (typically NIH stroke score <5)		

Stroke unit care and rehabilitation

Benefit of stroke unit care for stroke management is well established [5]. Following emergency management, all stroke patients who do not deserve intensive care are best managed in a stroke unit. Benefits of stroke units are independent of whether ischaemic or haemorrhagic stroke, time duration from onset to admission and age. Stroke unit provides specialized, coordinated multidisciplinary team care by the stroke team that consists of doctors, nurses, physiotherapists, occupational therapists, speech therapists, social service officers and counsellors or psychologists. Stroke team should carefully evaluate the patient and in the process of rehabilitation, should work towards achieving common goals that are decided at regularly held discussions, in agreement with the patient and family opinions where necessary. Goals should be measurable and achievable steps along the pathway to recovery. There should be an integration of stroke unit care with long term rehabilitation.

Management in a stroke unit involves evaluation of disabilities, assessment for co-morbidities, anticipation for complications and implementation of secondary prevention strategies. Swallowing assessment within the first 24 hours and managing hydration and nutrition, managing skin integrity and sphincter incontinence are important aspects of stroke nursing care. Initial chest physiotherapy, ensuring mobility, balance and preventing spasticity are important components of physiotherapy for stroke. Speech therapists supervise communication, and they are skilled in evaluating and managing swallowing disability. Occupational therapists will focus on activities of daily living and instrumental activities of daily living by improving hand functions and making use of adaptations. Social service officers will link the patient and family for their needs with the Department of Social Services and the counsellor assists grief management of the patient and the family.

Blood pressure management

Blood pressure is raised in 75% or more of stroke patients and is associated with poor outcome. Blood pressure management could be discussed based on several clinical scenarios: acute stroke awaiting thrombolysis with rtPA, thrombolysis ineligible acute ischaemic stroke, acute haemorrhagic stroke and long-term blood pressure control for secondary prevention. It is postulated that loss of autoregulation in acute stroke leads to development of high blood pressure which in turn could lead to cerebral oedema, increase haemorrhagic transformation in case of infarction and haematoma expansion in ICH and very low blood pressures could lead to increased infarction and peri-haematomal ischaemia.

In patients contemplating thrombolysis, blood pressure <185/110 mmHg and to maintain at 180/105 mmHg over the next 24 hours following the procedure is essential. The recommended intravenous medications to control blood pressure in the acute stage are labetalol, nicardipine and nitroprusside infusions. Upon achieving complete recanalization, particularly following clot retrieval, systolic blood pressure may be lowered to 120-140 mmHg to lower the risk of reperfusion haemorrhage. Caution should be taken to avoid relative hypotension during the procedure.

There is still uncertainty on the ideal blood pressure cutpoint for rtPA ineligible acute ischaemic stroke patients. Raised blood pressure in the acute stage may be beneficial to maintain perfusion to ischaemic penumbra and it spontaneously tends to decline over next 7 days. As very high blood pressure may be more hazardous it is recommended to lower blood pressure by 15%, if it is >220/120 mmHg

Based on available evidence, in the management of acute ICH with systolic blood pressure 150-220 mmHg, guidelines recommend aggressive blood pressure lowering to <140 mmHg for patients within 6 hours of symptom onset and no contraindications for acute blood pressure treatment. Aggressive blood pressure lowering with intravenous blood pressure lowering agents for 24 hours is recommended for a patient with ICH and systolic blood pressure $\geqq$ 220 mmHg. Hypertension is the most important modifiable risk factor in the secondary prevention of stroke. Blood pressure should be maintained <140/80 mmHg in all patients long term to minimize risk of development of all cerebrovascular diseases. In lacunar stroke where blood pressure lowering is most beneficial, lowering blood pressure <130/80 mmHg is recommended. Research studies have failed to show special benefits of any particular class of drugs.

Antiplatelets

Aspirin 160-300 mg given in the acute stage for ischaemic stroke has been shown to reduce mortality and recurrence of stroke by 14%. In patients with contraindications to aspirin a different antiplatelet agent could be considered. In instances where dysphagia exists, aspirin could be given per rectum or via nasogastric tube. Aspirin should not be given for patients awaiting thrombolysis or thrombectomy. Following thrombolysis with IV alteplase, commencement of aspirin is delayed by 24 hours. In situations where neurosurgery may be considered, such as in malignant middle cerebral artery occlusion, commencement of aspirin should be delayed. In patients presenting with minor stroke or TIA, a loading dose of aspirin 300 mg, followed by 75 mg daily for first 21 days with a loading dose of clopidogrel 300 mg on day one followed by 75 mg daily over next 90 days is recommended.

The benefits of antiplatelets for non-cardioembolic ischaemic stroke as a secondary preventive measure are well established. Recommended antiplatelets are aspirin,

dipyridamole and clopidogrel. When given long term, they reduce the risk of recurrence, myocardial infarction or of death by about 15-22%. Low dose aspirin (75-300 mg) as a single antiplatelet agent is effective, cheap and available. Clopidogrel 75 mg is slightly more effective than aspirin alone. The combination of aspirin and slow release dipyridamole is slightly more effective than aspirin alone. However slow release dipyridamole is not available in Sri Lanka. The combination of aspirin and clopidogrel has more haemorrhages and is not recommended except in the first 21 days following a TIA or a minor ischaemic stroke. The combination of aspirin and clopidogrel is appropriate for acute coronary syndrome or recent vascular stenting for a limited period of one year.

Anticoagulation

Both paroxysmal and persistent atrial fibrillation and rheumatic mitral valve disease with history of embolic event are well established risk factors for development of stroke following cardioembolism. Long term anticoagulation with warfarin or novel oral anticoagulants (NOVAC) is recommended in these patients.

Statins

The evidence for benefits of statins in acute ischaemic stroke is weak. However, it appears it is harmful to discontinue statins that the patient has been on prior to stroke. When given long term, statins are beneficial for primary prevention as well as reduction of both recurrence of ischaemic stroke and other cardiovascular events such as myocardial infarctions.

Note: Ideal control of blood sugar is important throughout hospital stay and long-term care. Further measures should be planned based on specific aetiology such as carotid dissection, carotid stenosis, haematological conditions, vasculitis, antiphospholipid syndrome etc.

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Conflicts of interest: none declared

ISSN 1391-0736

Printed by Ananda Press, Colombo.