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The Academy of Medicine, Singapore recently appointed an expert workgroup comprising gastroenterologists, general surgeons and anaesthesiologists to develop guidelines on the use of sedation during gastrointestinal (GI) endoscopy. The recommendations serve to guide clinical practice during sedation for GI endoscopy by non-anaesthesiologists in the hospital setting.

Proton-pump inhibitors (PPIs) are effective treatment for upper GI pathologies but their indiscriminate use could result in potential harms. A Singapore study had implemented a series of deprescribing interventions to curb PPI overutilisation, with findings supporting the safety of cautious deprescribing.

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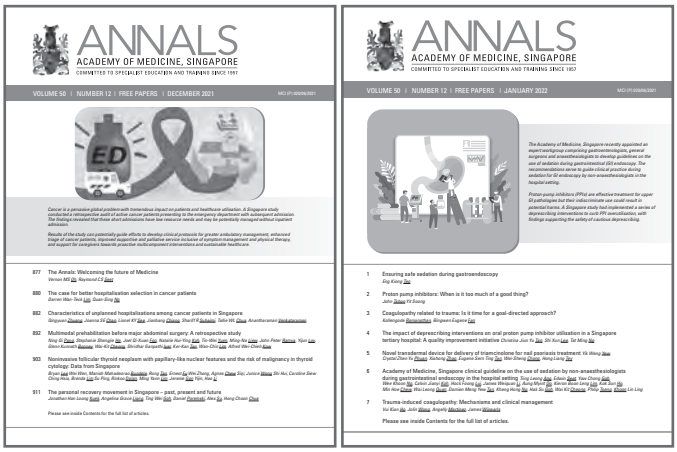
ANNALS

Official Journal of the Academy of Medicine, Singapore



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EDITORIAL

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Proton pump inhibitors: When is it too much of a good thing?

John Tshon Yit Soong [1,2] *PhD*

The popularity of proton pump inhibitors (PPIs) among both prescribers and patients may be ascribed to their relative low cost, efficacy and safety profile. Introduced in the late 1980s, PPIs are benzimidazole derivative drugs that inhibit the hydrogen-potassium ATPase exchanger ("the proton pump") on the luminal surface of the gastric parietal cell membrane.[1] The inhibition of the exchanger mechanism strongly decreases the secretion of protons needed for the secretion of hydrochloric acid. The PPIs are clinically indicated for peptic ulcer disease, gastroesophageal reflux, Zollinger-Ellison syndrome, non-steroidal anti-inflammatory drug (NSAID)-associated gut ulcers, and as a part of *Helicobacter pylori* eradication. Highly effective, their superiority over histamine-2 receptor antagonists (H2RAs)[2] is due in part to their ability to maintain gastric pH>4 reliably for up to 21 hours a day, but also to the phenomenon of tachyphylaxis observed in the action of H2RAs.[3]

However, PPIs are not a panacea for all ills. While not by any means conclusive, observational studies have suggested that long-term PPI use may be associated with important adverse effects.[4] Systemically, such use has been associated with increased risks of osteoporotic fractures; malabsorption of vitamin B_{12}, calcium, magnesium and iron; *Clostridium difficile* infection;[5] dementia; pneumonia; kidney disease; and stroke. The local observed effects of prolonged gastric acid suppression include hypergastrinemia, gastric atrophy and polyp formation, chronic *H. Pylori* infection,[6] and a potentially increased risk of gastric cancer.[7]

In Singapore, several studies have explored the magnitude of inappropriate PPI prescribing. A single-centre, point prevalence study found that 46.5% of hospitalised inpatients were prescribed a PPI, of which just over half (54.1%) did not have a US Food and Drug Administration (FDA) approved clinical indication.[8] Another Singapore study of hospitalised seniors (>65 years) suggests that the rate of potentially inappropriate prescribing of PPI is even higher in the elderly (up to 81.2%).[9]

With this context in mind, Tan et al. evaluate the effect of phased, multidisciplinary interventions to reduce PPI overutilisation at a tertiary hospital in Singapore, published in this issue of the *Annals*.[10] Sustained behaviour change is challenging. The team employed a framework by Anderson et al.[11] to target prescriber beliefs, knowledge and attitudes, as well as work environment and cultural factors, to "nudge" physicians towards intended behaviours. The first intervention was the introduction of a PPI deprescribing guide to 4 large prescribing departments within the hospital. The second intervention, introduced 10 months after the first, was the conducting of education sessions for internists at the hospital to highlight the potential harms of inappropriate PPI use.

The retrospective observational study utilised an interrupted time-series analysis to measure doses of oral PPI prescribed per 1,000 prescriptions every month, from 2013 to 2019, as a primary outcome. For safety analysis, the authors explored incident peptic ulcer disease per 1,000 patient-days for the hospital from 2015 to 2018. These calculations utilised routinely collected data as part of patient care within their hospital database. In addition, a case-notes review was undertaken for patients who had oral PPI deprescribed over a 5-month period (June to October 2017) to explore if restarting or escalation of PPI doses were needed within 6 months of discharge (N=262).

Interestingly, the study found that PPI utilisation rates were already declining before the first intervention (-77 daily doses/1,000 prescriptions a month, 95% confidence interval [CI] -105 to -52). This trend accelerated after the first intervention (-303 daily doses/1,000 prescriptions a month, 95% CI -474 to -131), but reversed after the second intervention (+405 daily doses/1,000 prescriptions a month, 95% CI 231 to 579). On deeper exploration, the rate of inpatient reduction in PPI prescription was steeper than outpatient prescription rates after the first intervention. However, after the second intervention, the rate of inpatient PPI prescriptions started to increase, and the rate

[1] National University Hospital, Singapore
[2] Yong Loo Lin School of Medicine, National University Singapore
Correspondence: Dr John Tshon Yit Soong, Division Advanced Internal Medicine, Tower Block 10th Floor, National University Hospital System, 1E Kent Ridge Rd, Singapore 119228.
Email: John_Soong@nuhs.edu.sg

of reduction in outpatient PPI prescription slowed. Overall, the study estimated a reduction of 1,930 daily doses/1,000 prescriptions a month, and a cost avoidance of SGD87,082 per year.

From the safety analysis, the rate of incident peptic ulcer disease did not change over time, and the case-notes review found that 62.6% of the patients had remained deprescribed of PPIs at 6 months after discharge. Of the 8.7% who died, none had a cause attributable to gastrointestinal bleeding. At least 10% of patients who had PPI treatment restarted had no clear indication documented.

Healthcare systems are dynamic and complex. Interventions rarely happen in isolation. Evaluation of interventions within real-life settings are necessary and meaningful. However, the inability to have rigorous control for environmental and patient factors (e.g. within a randomised clinical trial) often limits both the generalisability of outcomes, and causal inference. The interventions documented in the study occurred after a national campaign for deprescribing, which could explain the already declining rate of PPI prescriptions.

This study highlights the difficulties of enacting sustained behavioural change, and the challenges of measuring improvement and outcomes in the real-world clinical setting. The study utilises routinely collected data as part of patient care, to measure the primary outcome of PPI utilisation rates. This may be interpreted as a surrogate measure for the inappropriate prescribing of PPI. A "floor" effect is to be expected with this surrogate measure. Perfect performance would still produce a PPI prescription rate, though the latter would be clinically indicated. What this "target" should be is not clear, without adjustment for case-mix and clinical indication.

The methodology allows large amounts of data to be interrogated over time. However, as said data were not collected for the expressed purpose of answering this research question, it is subject to several limitations: information bias, not being comprehensive in terms of variables, inaccuracy of diagnostic and prescription coding, its retrospective nature, and having missing data elements not by chance. The study aimed to ameliorate these limitations by complementing the large data approach with a smaller case-notes review. While this study is limited to the acute hospital setting, it is expected that a large proportion of patients may have inappropriate PPIs prescribed in primary care and the community setting.

For a drug, efficacy is not clinical effectiveness. Real-world evaluations can provide meaningful answers to important questions about burden of disease, treatment adherence, cost-effectiveness, and health resource utilisation. Though with limitations, the study adds to our growing understanding of how we can better care for our patients.

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ORIGINAL ARTICLE

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Novel transdermal device for delivery of triamcinolone for nail psoriasis treatment

Yik Weng Yew *[1,2]*MBBS*, Crystal Zhen Yu Phuan *[1]*MRCP*, Xiahong Zhao [1]*PhD*, Eugene Sern Ting Tan [1]*MBBS (Singapore)*, Wei-Sheng Chong [1]*FAMS (Dermatology)*, Hong Liang Tey [1,2,3]*FAMS (Dermatology)*

ABSTRACT

Introduction: Nail psoriasis treatment is challenging due to difficult drug delivery and systemic therapy toxicities. Self-dissolvable microneedle patches embedded with corticosteroids offers a potentially rapid, minimally invasive drug delivery platform with good efficacy and minimal adverse side effects.

Methods: We conducted a 4-month prospective randomised controlled trial. Subjects with psoriatic nails were randomised to receive microneedle device delivered topical steroids on one hand and control treatment (topical Daivobet gel) on the other. Two independent dermatologists blinded to the treatment assignment scored their Nail Psoriasis Severity Index (NAPSI) during visits at baseline, 2 and 4 months. All treatment was discontinued after 2 months. Average NAPSI score on each hand was analysed.

Results: A total of 25 participants were recruited, aged 22 to 73 years. Majority were Chinese (72%), followed by Indian and Malay. There was equal randomisation of treatment to the left and right nail. While there was a rapid significant improvement in average NAPSI score for the control arm at 2 months, the treatment arm had a greater, more sustained improvement of the NAPSI score at 4 months. The average NAPSI score improved for both treatment and control group at 4 months compared to baseline. However, only the NAPSI value improvement in the controls at 2 months compared to baseline was statistically significant (P=0.0039). No severe adverse effects were reported.

Conclusion: To the best of our knowledge, this is the first prospective randomised control trial comparing microneedle technology against conventional topical steroids in nail psoriasis treatment. Our findings demonstrate microneedle technology is as efficacious as topical therapy.

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Keywords: Microneedle, nail, psoriasis

INTRODUCTION

Psoriasis is a chronic immune mediated inflammatory skin condition that affects about 2–4% of the Western populations, with rising incidence over the years.[1,2] The presentation of psoriasis varies from mild localised plaques to more severe erythrodermic forms, with plaque-type psoriasis being the most common. It frequently affects the skin and scalp, with up to one-third of patients with joint involvement[3] and over half with nail psoriasis.[4] Classical psoriatic nail lesions include nail plate pitting, onycholysis, nail bed discolouration, subungual hyperkeratosis and onychodystrophy. Pitting is the most common sign, followed by onycholysis;[5] but this may not be specific and can be seen in a variety of other nail conditions. The lifetime prevalence of nail involvement for psoriasis patients is estimated to be 80–90%[4] and this may present in the absence of cutaneous or joint disease in 5–10% of patients.[6] It is likely that the prevalence of nail psoriasis may be underestimated[7] and commonly overlooked as it is largely asymptomatic in the early stage, especially when patients experience more symptoms from their skin and joint involvement. However, early recognition is important for early intervention as nail psoriasis is considered an indicator for future or early psoriatic joint damage,[8] and can

[1] National Skin Centre, Singapore
[2] Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore
[3] Yong Loo Lin School of Medicine, National University of Singapore, Singapore
* Joint first authors
Correspondence: Dr Hong Liang Tey, National Skin Centre, Dermatology, Singapore 1 Mandalay Road, Singapore 308205.
Email: hltey@nsc.com.sg

CLINICAL IMPACT

What is New

- Microneedle patches are as effective as conventional topical steroid treatment at 4 months to serve as additional or alternative treatment for nail psoriasis.

Clinical Implications

- Self-application of our novel microneedle patches may improve delivery of care and healthcare outcomes for patients compared to intralesional triamcinolone injections that require physician administration and clinic visits.

be associated with longer disease duration, greater disease severity, and greater restrictions in activities of daily living. This can result in lower quality of life as measured with validated instruments such as Dermatology Life Quality Index (DLQI) and Nail Psoriasis Quality of life 10 (NPQ10).[9,10]

Routine evaluation and early treatment of nail involvement in psoriasis patients is therefore important. Patients should be evaluated in a holistic manner for severity of nail changes, as well as extent of skin and joint involvement. Nail psoriasis is known to be difficult to treat; current treatment modalities include topical therapy, intralesional therapy, photochemotherapy, laser therapy, radiotherapy and systemic therapy, including the use of biologics. Most importantly, patient education on general nail care measures is essential as some patients turn to manicuring practices such as artificial nails and nail extensions to conceal dystrophy, which may in turn irritate nails[11] and worsen their overall condition.

While topical therapy is a good initial option for patients with proximal nail matrix disease manifesting as pitting of the nails, it has limited efficacy for nail bed disease with subungual hyperkeratosis as topical therapy has suboptimal nail bed access. Beyond topical treatments, procedural therapies such as pulsed dye laser and intralesional corticosteroids have been investigated as possible treatment options. Monthly pulse dye laser therapy has limited efficacy, with long duration of treatment required.[12] Intralesional injection of corticosteroids can have moderate efficacy but requires in-person weekly injections by a physician for months.[13] The treatment is very painful, precluding its routine use. Further treatment options such as oral systemic and biologic therapies have been found to be effective but the potential associated adverse side effects limit their use to patients with concurrent more severe cutaneous involvement.[14] Patients are often fatigued, due to poor efficacy of various treatment modalities and failure to comply to long-term treatments with topical agents. The treatment of nail psoriasis remains challenging due to great difficulty in drug delivery to site of action and possible toxicities of most conventional systemic therapies. With the advent of a new transdermal drug delivery platform in the form of microneedle technology,[15] the option of a rapid and painless drug delivery to the nail matrix is promising. To investigate the therapeutic effects and advantages of using microneedle technology to deliver topical corticosteroids to psoriatic nails in a rapid and painless way, we conducted a prospective, randomised controlled study to compare microneedle technology with current conventional topical steroid treatment in the treatment of nail psoriasis.

METHODS

We conducted a 4-month prospective randomised controlled trial in National Skin Centre, a tertiary dermatology centre in Singapore to evaluate treatment response of nail psoriasis following treatment with a self-dissolving microneedle drug delivery patch to administer topical steroids to psoriatic nails. We included all adult patients, aged 21 years and above, with nail psoriasis affecting both hands in varying severity, diagnosed by certified dermatologists. All patients recruited also had classical chronic plaque psoriasis diagnosed by dermatologists. There was consideration of alternative differentials for 2 of the patients. However, their fungal nail microscopy and culture performed were negative, suggesting that the diagnosis of onychomycosis was unlikely. The study excluded those with unilateral nail psoriasis present on one hand had previous localised phototherapy to their nails, oral systemic agents, biologics or have a history of allergy to alcohol swabs, steroids or hyaluronic acid. Patients with recent topical treatment of nails or who were undergoing whole body narrow band ultraviolet B therapy were included but were advised to maintain symmetrical positioning during treatment. All patients underwent a fingernail clipping for microscopy to rule out onychomycosis before enrolment in the study.

This was a left to right intrapatient comparison trial where study participants received sterile microneedle topical steroids treatment on 1 hand and control treatment (topical Daivobet gel containing 50µg/g calcipotriol and 500µg/g betamethasone, as dipropionate) on the other hand. Randomisation was performed for each participant to determine treatment allocation for 2 hands. This was done with a computer-generated sequence by a dedicated person who had no further

involvement in the rest of the study. Patients were taught by research assistants on the way to administer the treatment patch and control treatment.

These dissolving microneedle patches (Fig. 1) were made of sodium hyaluronate as water-soluble matrix material with a total of 0.5mg triamcinolone embedded in the distal 50% of the microneedles. The microneedles are 600μm in length and pyramidal in shape. They are prepared via a micromould-based method with a stainless steel master structure consisting of 225 pyramidal needles created using an electrical discharge machining process. The total amount of triamcinolone (0.5mg) in each microneedle patch to be applied twice weekly was calculated based on the weekly dosage of up to a maximum of 0.1mL of 10mg/mL injected to proximal nail folds in reported literature.[16] Alcohol swabs were provided to wipe the nail fold prior to application. The microneedle patches were being held in place over the nail fold area with a nail patch applicator clip (Figs. 2 and 3).

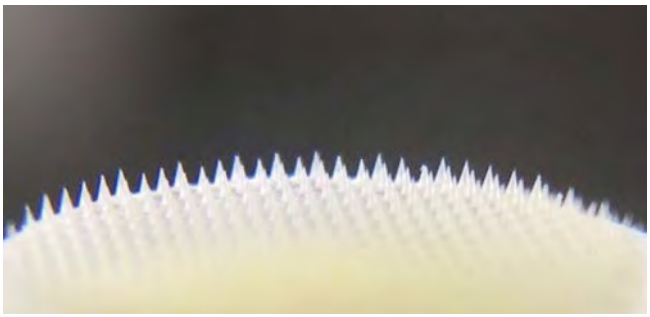

Fig. 1. Microneedle self-dissolving patch.

To assess the severity of psoriatic nail disease, Nail Psoriasis Severity Index (NAPSI) was used in our study. Being one of the most comprehensive assessment tools of psoriatic nail disease used in clinical trials,[17] it has been validated as a numeric, reproducible, objective and simple tool for evaluation of treatment response of psoriatic nails. In this system, the nail is divided into 4 quadrants and 1 point is awarded if there is any finding of nail matrix and 1 for nail bed change that is seen, per quadrant, or 0–8 per nail. Nail matrix psoriasis was assessed by the presence of any feature of nail matrix psoriasis, including nail pitting, leukonychia, red spots in the lunula, and crumbling in each quadrant of the nail. Nail bed psoriasis was assessed by the presence of features such as onycholysis, oil drop (salmon patch) dyschromia, splinter haemorrhages, and nail bed hyperkeratosis in each quadrant of the nail. NAPSI scoring was administered by 2 independent

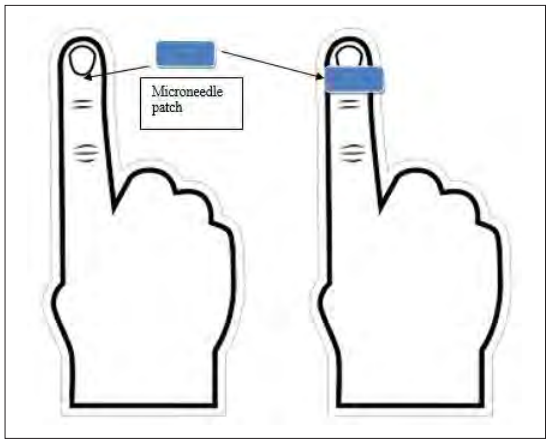

Fig. 2. Application of microneedle patch over horizontal nail fold.

Fig. 3. Clinical photograph of application of nail patch applicator clip.

dermatologists blinded to the treatment assignment at baseline and follow-up visits (2-month and 4-month visits). The average NAPSI nail score of the affected nails on each hand was analysed. This was calculated from the total NAPSI nail score of psoriasis-affected nails divided by the number of affected nails. Other clinical information such as Psoriasis Area Severity Index (PASI), Dermatology Life Quality Index (DLQI) and NPQ10 were measured at baseline and follow-up visits. All recruited patients were reviewed at baseline and at 2 and 4 months after treatment initiation. All treatment was discontinued after 2 months. The study concluded after the third visit (4 months) and all patient information was collated. Any localised side effects to the fingers were also recorded during the follow-up visits.

In previous studies,[18,19] patients recruited at baseline from a population with psoriatic nails had a mean NAPSI nail score of about 6 with a standard deviation of 2. Based on the assumption that patients recruited for our study will have similar baseline scores for both the case and control groups, we expect a 1–1.5 point score difference in nail changes between active and control groups after 4 months of treatment at the end of the study. Based on these assumptions, a sample size of 16–34 is required to detect 1–1.5 point score difference in nail changes between the 2 groups with statistical power of 80%, at 5% significance level. Hence, a sample size of 20 patients was decided to achieve the above statistical power at 5% significance level. The primary outcome of this study was NAPSI scores, and secondary outcomes were PASI, DLQI and NPQ10 scores, all measured at the 2-month and 4-month follow-up visits. Differences between the active against control group, as well as differences between study visits within each treatment group were reported in medians with ranges and means with standard deviations (SD). Wilcoxon signed-rank test was used to compare differences. Statistical significance was assessed at a level of 0.05. All statistical analysis were performed using R version 3.5.3 software. The above study design and methods were approved the Singapore institute ethics board prior to initiation.

RESULTS

A total of 25 patients were recruited for the study, and their demographic characteristics were shown in Table 1. They were aged 22 to 73 years with most of them being males (76.0%). Majority of the patients were Chinese (72%), followed by Indians (3%) and Malays (3%). There was approximately equal randomisation of treatment to the left (48%) and right nail (52%). Four study participants did not complete the third study visit as they were either lost to follow-up or could not complete their follow-up due to COVID-19 visit restrictions.

There was a rapid significant improvement in average NAPSI score for the control arm at 2 months, while the treatment arm with microneedles had a more sustained and greater improvement of the NAPSI score at 4 months (Fig. 4). The average NAPSI score improved for both the treatment and the control arm in the third visit compared to the first visit, but only the improvement of the NAPSI value in the control group at 2 months compared to baseline was statistically significant (P=0.004) (Table 2). The control group showed higher improvement at 2 months compared with the treatment group but the improvements at 4 months for both groups were similar (Table 3). These findings reflect that treatment with microneedle patches are at least as effective as the conventional topical steroid treatment. In addition, more than half of patients (52%) indicated a score of at least 7 when asked to rate their willingness to use the microneedle patch if it was available in the market on a scale of 0 to 10. All patients were monitored for adverse events (AE) with only 1 patient with missing AE data. Of the 9 (37.5%) patients who reported AE, 7 reported pain, 1 reported discomfort with the clip, 1 reported peeling skin and 1 reported numbness. Of the 7 patients who reported pain, none reported a pain score exceeding 2 out of 10. The Koebner phenomenon was not observed at the nail folds where microneedles were applied. The overall psoriasis severity remained similar throughout the 4-month study period with similar PASI scores for all 3 visits. However, it was noted that there was a significant decrease in DLQI scores from baseline to 2 months as the study participants received localised therapies targeted to their nails. (Table 4).

Table 1. Demographics of study participants

Characteristics	**n=25**
Age, years	
Median (range)	43 (22–73)
Mean (SD)	43.28 (14.44)
Sex, no. (%)	
Male	19 (76.0%)
Female	6 (24.0)
Race, no. (%)	
Chinese	18 (72.0)
Malay	3 (12.0)
Indian	3 (12.0)
Others	1 (4.0)
Randomisation, no. (%)	
Treatment: Left nail	12 (48.0)
Treatment: Right nail	13 (52.0)

SD: standard deviation

DISCUSSION

Nail psoriasis is prevalent in both psoriasis and psoriatic arthropathy. There is recent increased emphasis on treatment as nail psoriasis is increasingly recognised to have negative impacts on the quality of life and ability

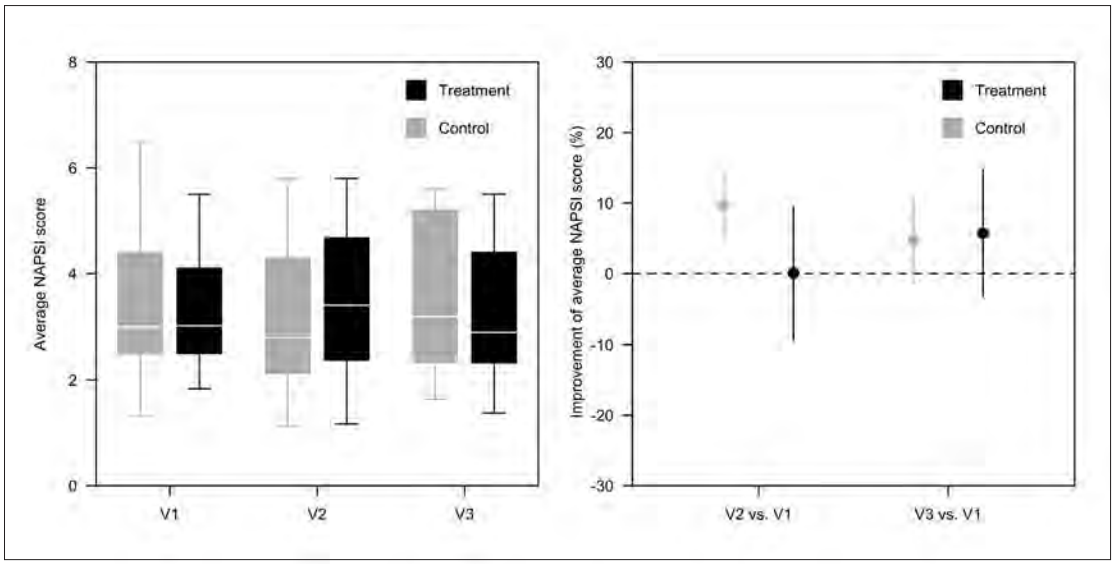

Fig. 4. Comparison of average Nail Psoriasis Severity Index (NAPSI) scores between treatment and control arms across baseline (V1) and follow-up visits (V2 and V3).
V: visit

to perform daily activities. With limitations to current therapy methods due to poor penetration,[20] tedious administration and side effects, microneedle technology for drug delivery has come into focus. This is especially relevant in psoriasis, where keratinocyte hyperproliferation causes the formation of prominent plaques that further hinders transdermal delivery. Microneedles can potentially serve as a method of drug delivery considered superior to conventional transdermal delivery as it is known to be minimally invasive, painless, convenient and promotes improved patient compliance.[21] So far, the use of microneedles has been tested with the administration of methotrexate,[22,23] cyclosporin[24,25] and biologics[26,27] such as anti-TNF-alpha antibody, with good results and minimal side effects. The use of a hyaluronic acid-based microneedle patch had previously been examined in a pilot open trial to treat psoriatic plaques with promising results, but evidence on microneedle patches to treat psoriatic nails is lacking.[28]

Our findings demonstrate that treatment with microneedle patches were at least as effective as conventional topical steroid treatment. The conventional topical steroids treatment had demonstrated a rapid better treatment response compared to the microneedle treatment. While the observed higher NAPSI score at visit 2 for treatment arm was not statistically significant (Table 2), the significantly better improvement scores at visit 2 for control group compared to treatment group could be attributed to a possible delay in any treatment effects from the microneedle compared to the control treatment. Nevertheless, any visible treatment effects seem to be similar between the 2 treatment arms after 4 months, suggesting that the microneedle treatment might have a slower onset or the effects could

Table 2. Average NAPSI score within each group across baseline (V1) and follow-up visits (V2 and V3)

	V1 (n=5)	**V2 (n=5)**	**V3 (n=21)**	***P* value (V2 vs V1)**	***P* value (V3 vs V1)**
Treatment					
Median (range)	3.02 (1.83–5.5)	3.4 (1.17–5.8)	2.9 (1.38–5.5)	0.90	0.06
Mean (SD)	3.42 (1.19)	3.42 (1.39)	3.31 (1.39)		
Control					
Median (range)	3 (1.32–6.5)	2.8 (1.12–5.8)	3.2 (1.63–5.6)	0.004	0.10
Mean (SD)	3.54 (1.45)	3.22 (1.41)	3.53 (1.39)		

NAPSI: Nail Psoriasis Severity Index; SD: standard deviation; V: visit

Table 3. Percentage improvement of NAPSI scores at follow-up visits (V2 and V3) from baseline (V1)

	V1 (n=25) %	V2 (n=25) %	V3 (n=21) %
Treatment			
Median (range)	3.02 (1.83–5.5)	-2.5 (-37.5–50)	6.38 (-58.18–41.32)
Mean (SD)	3.42 (1.19)	0.07 (24.34)	21; 5.71 (21.26)
Control			
Median (range)	3 (1.32–6.5)	9.3 (-16.67–37.5)	3.45 (-28–36.8)
Mean (SD)	3.54 (1.45)	9.68 (12.84)	21; 4.73 (14.72)
P value	0.13	0.02	0.84

NAPSI: Nail Psoriasis Severity Index; SD: standard deviation

Table 4. Quality of life markers: PASI, DLQI, NPQ10 across baseline (V1) and follow-up visits (V2 and V3)

	V1	V2	V3	*P* value (V2 vs V1)	*P* value (V3 vs V1)
PASI	n=24	n=23	n=20		
Median (range)	1.65 (0–20.1)	1 (0–10.7)	1.9 (0–17.4)	0.26	0.58
Mean (SD)	2.86 (4.60)	2.23 (3.02)	2.92 (4.18)		
DLQI	n=25	n=24	n=20		
Median (rrange)	4 (0–24)	2 (0–19)	3.5 (0–27)	0.02	0.33
Mean (SD)	6.16 (5.75)	4.25 (5.02)	6.10 (7.52)		
NPQ10	n=25	n=24	n=19		
Median (range)	0 (0–14)	0 (0–14)	0 (0–15)	0.86	0.89
Mean (SD)	1.40 (2.96)	1.54 (2.98)	1.84 (3.58)		

DLQI: Dermatology Life Quality Index; NPQ10: Nail Psoriasis Quality of life 10; PASI: Psoriasis Area Severity Index; SD: standard deviation

possibly be more persistent.

Various matrix materials have been utilised in previous studies to examine the efficacy of drug delivery. Our study used hyaluronic acid as the matrix material for the microneedles in view of its excellent biological properties of biodegradability and non-immunogenicity. The self-dissolvable hyaluronic acid microneedle patch loaded with corticosteroids provides enhanced drug delivery to the nails. These microneedle patches have micron-scale needles that can permeabilise the stratum corneum by creating microchannels in the skin, thereby allowing the embedded corticosteroids to penetrate the nail matrix and bed. These microneedles are long enough to pierce through the barrier but short enough to avoid causing pain. We observed that the treatment arm with microneedles had a more sustained and greater improvement of the NAPSI score at 4 months, but this was not statistically significant. This might be related to the need for a larger sample size or a longer duration of follow-up for the clinical trial.

A strength of this study is its intrapatient design where each patient served as his own case and control for treatment response, which reduces the possible confounders to treatment response. In addition, patients with recent prior treatment with systemic effects were excluded. Our study demonstrates that microneedle patches have the potential to serve as an important adjunct treatment option for nail psoriasis, an alternative to topical therapy, and even intralesional triamcinolone injections. With the potential for self-application of microneedle patches at home, patients have the convenience of home therapy. This will be ideal for patients with busy schedules who are not able to make regular clinic visits for triamcinolone injections. There

will also be potential time and cost savings as patients need not make multiple clinic visits. Delivery of care to patients and their healthcare outcomes are also likely to improve. Most patients reported no adverse outcomes from applying the nail microneedles and most adverse effects were limited to during the application process. In addition, better designed or customised nail fold applicators could be considered for improved fitting and less discomfort for application.

One of the main limitations of this study is the lack of long-term follow-up, as it is possible that nail dystrophy can relapse just like psoriasis. Furthermore, given the natural speed of nails growth, there might be a lag in any visible nail improvement. Since all treatment was concluded in 2 months but followed up for 4 months, this limited duration might have limited the efficacy of each treatment. Conversely, possible longer-term side effects of microneedle use not observed in this study include infection, irritant contact dermatitis, allergic contact dermatitis, post-inflammatory hyperpigmentation, abnormal scarring, and irritant and allergic granulomas.[29] A longer duration of treatment and follow-up could show more promising results with the microneedle patch. Further studies with a larger sample size could be performed by expanding on this pilot trial to detect smaller treatment differences with adequate statistical power.

CONCLUSION

To the best of our knowledge, this is the first prospective randomised control trial comparing the efficacy of microneedle technology against current conventional topical steroid treatment in the treatment of nail psoriasis. While new biologic therapies effective for both plaque psoriasis and psoriatic arthritis are promising for the treatment of nail psoriasis, topical treatments should still be the first-line therapy especially in individuals who have predominantly nail psoriasis with limited systemic involvement. Further research with larger sample sizes is required to further support the use of microneedles to fill treatment gaps in terms of optimal dose adjustments and application frequency, as part of clinical management of nail psoriasis and for further development in this drug delivery field.

Disclosure

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EDITORIAL

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Ensuring safe sedation during gastroendoscopy

Eng Kiong Teo [1] *MRCP (UK), FRCP (Edin), FAMS*

Gastrointestinal (GI) endoscopy started in Singapore in 1968 with diagnostic endoscopic gastric examination, using flexible fibre-optics GI endoscopy. Fibre-optic flexible sigmoidoscopy and colonoscopy were introduced later. Most of these procedures were performed then without sedation. The patients needed to cooperate with the endoscopists and inability to complete the endoscopic examination was common then due to intolerability of the procedure. By the 1980s, therapeutic GI endoscopy was introduced and subsequently practised as a standard of care. Since then, we have seen an expansion in the scope of therapeutic endoscopic procedures. With the increasing complexity of endoscopic procedures requiring a longer procedure time, moderate sedation during GI endoscopy becomes an inherent component for both patient comfort and patient safety as well as procedural success. Although some patients may opt for GI endoscopy without sedation, the vast majority of GI endoscopic procedures are currently performed under moderate sedation.

The training to administer moderate sedation is incorporated into the training curriculum of GI endoscopy. Trainees are taught the agents used to induce moderate sedation and the medications needed to reverse the sedation when needed. Common agents to induce moderate sedation are benzodiazepines and opiates used either singly or in combination. Endoscopists are also taught to assess and recognise the risks of moderate sedation. These include hypoventilation and haemodynamic instability. Although the administration of moderate sedation is an integral component of endoscopic training, there was no defined module and no distinct certification for privileges to administer moderate sedation until the 2000s. In the early 2000s, Singapore healthcare system embarked on a journey of improvement and accreditation. The Joint Commission International (JCI) accreditation system was selected by many private and public healthcare institutions. Applying the standards of JCI, endoscopists (and others who perform moderate sedation) must show proof of competency for both administration of the agents, the use of reversal agents, and the ability to administer advanced airway and cardiopulmonary life support. Since then, endoscopists performing endoscopy under moderate sedation need to be certified at regular intervals to ensure the currency of their knowledge and skills in administration of moderate sedation.

Apart from the endoscopist, moderate sedation can be administered by the anaesthetist as well. In fact, the administration and monitoring of patients under moderate sedation is part of the curriculum for the training of anaesthesiology. Although the risk for mortality and other adverse events are less when compared to general anaesthesia, there is still a definite risk of over-sedation leading to hypoventilation and hypoxaemia. In addition, some of the agents used in moderate sedation can cause hypotension or bradycardia, leading to increased risk of stroke and acute myocardial infarction especially in patients with significant relevant comorbidities. As a result of adverse outcomes due to sedation, the Ministry of Health in Singapore commissioned the Academy of Medicine, Singapore (AMS) to provide guidelines on safe sedation practice for non-anaesthesiologists in medical clinics, stand-alone ambulatory surgical centres and stand-alone endoscopy suites in Singapore. This guideline was published on 19 May 2014 and recently updated in July 2021. This guideline formed the basis of many of our current practices in the administration of moderate sedation.[1] The guideline outlines the need for pre-sedation assessment and to consider the engagement of an anaesthesiologist should the risk be high and/or the procedure is expected to be prolonged. The American Society of Anesthesiologists (ASA) score was recommended and airway assessment was also included so as to anticipate difficulty in securing definitive airway should the need arise. These pre-sedation assessments aimed at detecting patients with the highest risk for moderate sedation so that additional resources, e.g. an anaesthetist, can be channelled to these patients. For the patients without high risks for moderate sedation, the endoscopist and the endoscopic nurse, trained in the administration and monitoring of moderate sedation, will suffice. This is to ensure that the cost of endoscopic examination remained affordable while balancing the risk of adverse events.

[1] Department of Medicine, Sengkang General Hospital, Singapore
Correspondence: Prof Eng Kiong Teo, Department of Medicine, Sengkang General Hospital, 110 Sengkang East Way, Singapore 544886.
Email: teo.eng.kiong@singhealth.com.sg

The guideline on moderate sedation published by AMS in 2014 specifically mentioned the use of propofol separately from other agents used for moderate sedation. The 2014 guideline recommended that propofol must be administered by an anaesthesiologist. This is because the experience with the use of propofol then for endoscopic procedures was limited and there was no reversal agent if a patient is over-sedated with propofol. In addition, propofol has a narrow therapeutic window, magnifying the risk of over-sedation and hypoventilation. However, propofol has significant pharmacological advantages over benzodiazepines. Unlike benzodiazepines, propofol is short-acting and does not have active metabolites that prolong the sedative effects after the endoscopic examination. Patient who received propofol for sedation recover more rapidly compared to those who received benzodiazepines. This study also showed that a nurse as a trained sedationist can effectively and safely administer the propofol and monitor the patient adequately.[2] With these data on propofol,[3-6] endoscopists in Singapore have also started using propofol as an agent for moderate sedation. These procedures are performed in endoscopy suites in the hospital setting where appropriate facilities and adequate manpower are available. The experience by many local endoscopists in Singapore mirrors that described in the reports in Western endoscopic centres.

In 2021, AMS revised the guidelines for sedation, and sedation for GI endoscopy was discussed separately. A workgroup consisting of representatives from the College of Anaesthesiologists, College of Surgeons and the Chapter of Gastroenterologists came together to review the available information and developed the guideline for sedation for GI endoscopy in the hospital setting. Current evidence was reviewed and were graded for the recommendations. This guideline seeks to update the community of endoscopists on current practices, with the primary aim of patient safety and secondary aim of providing a sustainable system without significant compromise on patient safety. This guideline covers multiple areas including consent, training requirements, agents available and the knowledge required to use these agents, use of reversal agents, monitoring of patients, and resuscitative competencies should the patient develop ventilatory or haemodynamic instability.[7]

It is the aim of AMS to offer professional guidance so that specialists can provide care with confidence that they are within international standards. This guideline on sedation in GI procedures is one such initiative. AMS as a professional body will continue to provide guidance so that Singapore can maintain its leadership in standards of medical care in the Asia-Pacific region.

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EDITORIAL

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Proton pump inhibitors: When is it too much of a good thing?

John Tshon Yit Soong [1,2] *PhD*

The popularity of proton pump inhibitors (PPIs) among both prescribers and patients may be ascribed to their relative low cost, efficacy and safety profile. Introduced in the late 1980s, PPIs are benzimidazole derivative drugs that inhibit the hydrogen-potassium ATPase exchanger ("the proton pump") on the luminal surface of the gastric parietal cell membrane.[1] The inhibition of the exchanger mechanism strongly decreases the secretion of protons needed for the secretion of hydrochloric acid. The PPIs are clinically indicated for peptic ulcer disease, gastroesophageal reflux, Zollinger-Ellison syndrome, non-steroidal anti-inflammatory drug (NSAID)-associated gut ulcers, and as a part of *Helicobacter pylori* eradication. Highly effective, their superiority over histamine-2 receptor antagonists (H2RAs)[2] is due in part to their ability to maintain gastric pH>4 reliably for up to 21 hours a day, but also to the phenomenon of tachyphylaxis observed in the action of H2RAs.[3]

However, PPIs are not a panacea for all ills. While not by any means conclusive, observational studies have suggested that long-term PPI use may be associated with important adverse effects.[4] Systemically, such use has been associated with increased risks of osteoporotic fractures; malabsorption of vitamin B_{12}, calcium, magnesium and iron; *Clostridium difficile* infection;[5] dementia; pneumonia; kidney disease; and stroke. The local observed effects of prolonged gastric acid suppression include hypergastrinemia, gastric atrophy and polyp formation, chronic *H. Pylori* infection,[6] and a potentially increased risk of gastric cancer.[7]

In Singapore, several studies have explored the magnitude of inappropriate PPI prescribing. A single-centre, point prevalence study found that 46.5% of hospitalised inpatients were prescribed a PPI, of which just over half (54.1%) did not have a US Food and Drug Administration (FDA) approved clinical indication.[8] Another Singapore study of hospitalised seniors (>65 years) suggests that the rate of potentially inappropriate prescribing of PPI is even higher in the elderly (up to 81.2%).[9]

With this context in mind, Tan et al. evaluate the effect of phased, multidisciplinary interventions to reduce PPI overutilisation at a tertiary hospital in Singapore, published in this issue of the *Annals*.[10] Sustained behaviour change is challenging. The team employed a framework by Anderson et al.[11] to target prescriber beliefs, knowledge and attitudes, as well as work environment and cultural factors, to "nudge" physicians towards intended behaviours. The first intervention was the introduction of a PPI deprescribing guide to 4 large prescribing departments within the hospital. The second intervention, introduced 10 months after the first, was the conducting of education sessions for internists at the hospital to highlight the potential harms of inappropriate PPI use.

The retrospective observational study utilised an interrupted time-series analysis to measure doses of oral PPI prescribed per 1,000 prescriptions every month, from 2013 to 2019, as a primary outcome. For safety analysis, the authors explored incident peptic ulcer disease per 1,000 patient-days for the hospital from 2015 to 2018. These calculations utilised routinely collected data as part of patient care within their hospital database. In addition, a case-notes review was undertaken for patients who had oral PPI deprescribed over a 5-month period (June to October 2017) to explore if restarting or escalation of PPI doses were needed within 6 months of discharge (N=262).

Interestingly, the study found that PPI utilisation rates were already declining before the first intervention (-77 daily doses/1,000 prescriptions a month, 95% confidence interval [CI] -105 to -52). This trend accelerated after the first intervention (-303 daily doses/1,000 prescriptions a month, 95% CI -474 to -131), but reversed after the second intervention (+405 daily doses/1,000 prescriptions a month, 95% CI 231 to 579). On deeper exploration, the rate of inpatient reduction in PPI prescription was steeper than outpatient prescription rates after the first intervention. However, after the second intervention, the rate of inpatient PPI prescriptions started to increase, and the rate

[1] National University Hospital, Singapore
[2] Yong Loo Lin School of Medicine, National University Singapore
Correspondence: Division Advanced Internal Medicine, Tower Block 10th Floor, National University Hospital System, 1E Kent Ridge Rd, Singapore 119228.
Email: John_Soong@nuhs.edu.sg

of reduction in outpatient PPI prescription slowed. Overall, the study estimated a reduction of 1,930 daily doses/1,000 prescriptions a month, and a cost avoidance of SGD87,082 per year.

From the safety analysis, the rate of incident peptic ulcer disease did not change over time, and the case-notes review found that 62.6% of the patients had remained deprescribed of PPIs at 6 months after discharge. Of the 8.7% who died, none had a cause attributable to gastrointestinal bleeding. At least 10% of patients who had PPI treatment restarted had no clear indication documented.

Healthcare systems are dynamic and complex. Interventions rarely happen in isolation. Evaluation of interventions within real-life settings are necessary and meaningful. However, the inability to have rigorous control for environmental and patient factors (e.g. within a randomised clinical trial) often limits both the generalisability of outcomes, and causal inference. The interventions documented in the study occurred after a national campaign for deprescribing, which could explain the already declining rate of PPI prescriptions.

This study highlights the difficulties of enacting sustained behavioural change, and the challenges of measuring improvement and outcomes in the real-world clinical setting. The study utilises routinely collected data as part of patient care, to measure the primary outcome of PPI utilisation rates. This may be interpreted as a surrogate measure for the inappropriate prescribing of PPI. A "floor" effect is to be expected with this surrogate measure. Perfect performance would still produce a PPI prescription rate, though the latter would be clinically indicated. What this "target" should be is not clear, without adjustment for case-mix and clinical indication.

The methodology allows large amounts of data to be interrogated over time. However, as said data were not collected for the expressed purpose of answering this research question, it is subject to several limitations: information bias, not being comprehensive in terms of variables, inaccuracy of diagnostic and prescription coding, its retrospective nature, and having missing data elements not by chance. The study aimed to ameliorate these limitations by complementing the large data approach with a smaller case-notes review. While this study is limited to the acute hospital setting, it is expected that a large proportion of patients may have inappropriate PPIs prescribed in primary care and the community setting.

For a drug, efficacy is not clinical effectiveness. Real-world evaluations can provide meaningful answers to important questions about burden of disease, treatment adherence, cost-effectiveness, and health resource utilisation. Though with limitations, the study adds to our growing understanding of how we can better care for our patients.

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EDITORIAL

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Coagulopathy related to trauma: Is it time for a goal-directed approach?

Kollengode Ramanathan [1]*FCICM*, Bingwen Eugene Fan [2]*MRCP*

Trauma represents a leading cause of death globally, and post-traumatic haemorrhage accounts for 40% of early mortality in spite of recent improvements in modern trauma care.[1] Post-traumatic haemorrhage occurs primarily from direct injury to blood vessels, leading to exsanguination and hypovolaemic shock depending on the type and calibre of the affected vessels. However, one-third of patients with major trauma develop secondary injury from microvascular haemorrhage due to coagulopathy associated with trauma, the pathogenesis of which is multifactorial.[2,3] Other terminologies that have been proposed to identify this pathological entity include trauma-induced coagulopathy (TIC), trauma-associated coagulopathy, early coagulopathy of trauma, acute traumatic coagulopathy, acute coagulopathy of trauma shock, and coagulopathy of trauma.[1,4] It is also established that TIC is a multiphenotypic disease state that incorporates coagulation and inflammation cascades. The condition results in impaired clot formation, breakdown, and overall poor vascular homeostasis, contributing to early transfusion requirements, multiorgan failure and mortality.[4]

In this issue of the *Annals*, Ho et al. present an updated and comprehensive narrative review of literature on coagulopathy associated with trauma. It covers pathophysiology of the condition and emerging advances in management, including rapid diagnosis and goal-directed therapy.[5] The review is based on a literature search using robust selection of keywords pertaining to coagulopathy of trauma, updated until October 2020. The researchers have highlighted the burning controversies in the area, including the evidence for viscoelastic haemostatic assay-targeted therapy versus the fixed ratio massive transfusion protocols, and outlined some of the ongoing randomised controlled trials whose results are eagerly awaited. However, there are a few aspects of coagulopathy of trauma not covered within the primary aims of the review article and need special mention. The pathophysiological complexities highlighted in the review are further magnified by the lack of uniform definition of TIC, as well as knowledge gaps in the management of a haemorrhagic trauma patient.

The authors summarised that the pathophysiology of coagulopathy of trauma can be dynamic.[5] Polytrauma patients manifest diverse phenotypes of coagulopathy ranging from hypo- to hyper-coagulability and may quickly shuffle between phenotypes.[6] In addition to hyperfibrinolysis and fibrinolysis shutdown, endothelial activation, as well as platelet and fibrinogen dysfunction, also occurs in severely injured patients, worsening the secondary coagulopathy. Nevertheless, the review article does not highlight the challenges pertaining to the definition of coagulopathy of trauma. A recent communication by the International Society on Thrombosis and Haemostasis (ISTH) Scientific and Standardization Committee on fibrinolysis, disseminated intravascular coagulation, and perioperative and critical care thrombosis and haemostasis, was published in 2020. The article highlighted the need for a standard definition of TIC while accepting the limitations on timing of blood sampling, as well as not having a standard laboratory method to diagnose and prognosticate it.[4] The definition of TIC is incomplete by virtue of the variable magnitude of presentation, the early resuscitative practices during the period of tissue injury and shock, in addition to its complex pathophysiology. The committee stratified clinical presentation of TIC as primary versus secondary, early versus late, enhanced versus inhibited fibrinolysis, and responders versus non-responders, in what can be considered as a step forward towards defining this phenomenon.

TIC comprises complex haemostatic dysfunction with likely multiple interrelated pathways, making standard laboratory tests (SLTs) (e.g. international normalised ratio [INR], prothrombin time [PT] and activated partial thromboplastin time [PTT]) poorly reflective of the underlying pathophysiologic processes. While deranged INR is regarded as a major predictor of death and intensive care unit (ICU) length of stay in patients with severe trauma, coagulopathy of trauma can also

[1] Cardiothoracic Intensive Care Unit, National University Hospital, Singapore
[2] Department of Haematology, Tan Tock Seng Hospital, Singapore
Correspondence: Dr Kollengode Ramanathan, Cardiothoracic Intensive Care Unit, Level 2, Main Building, 1E Kent Ridge Road, National University Heart Centre, National University Hospital, Singapore 119228.
Email: ram_ramanathan@nuhs.edu.sg

occur in patients with normal PT/INR and PTT values.[1,4] However, the emergence of point-of-care tests such as viscoelastic haemostatic assays (VHAs) provides a global approach to evaluating coagulopathy of trauma as compared to SLTs. While SLTs are universally available, they have a longer turnaround analytic time and are primarily designed to evaluate the short initial phase of secondary haemostasis (thrombin generation and formation of a fibrin clot). They do not reflect platelet function and hyper-fibrinolytic activity well. On the other hand, VHAs are point-of-care tests that can yield quicker results and detect the dynamics, stability and sustainability of clot formation, as well as early fibrinolysis. However, VHAs are still unable to provide a sensitive reflection of impaired platelet function. Platelet function remains poorly monitored during trauma resuscitation and while platelet dysfunction has been associated with worse outcomes in trauma, the mechanisms by which platelet dysfunction contributes to coagulopathy are poorly understood.[6] Ho et al. have highlighted the results of the recently published Implementing Treatment Algorithms for the Correction of Trauma-Induced Coagulopathy (iTACTIC) multicentre randomised controlled trial, which compared the use of VHA-guided to SLT-guided transfusion in adult trauma patients with haemorrhagic shock.[7] The trial showed no differences in survival or transfusion requirements if they were randomised to the SLT or the VHA arm, as well as in the secondary outcomes (mortality, ventilator-free days, ICU-free days and hospital length of stay). While the iTACTIC trial showed a significant reduction in the timing of interventions in the VHA group, secondary outcomes and post hoc analyses were not adjusted for multiple comparisons. A stepwise sequential VHA algorithm, similar to the one highlighted by Ho et al.,[5] might have been worthwhile looking into in a trauma resuscitation setting. On the contrary, the only other randomised controlled trial that compared SLTs to VHAs in major trauma showed survival benefits with reduction in transfusion requirements.[8] While the authors have highlighted the major findings from existing randomised controlled trials, the bottom line remains that there is a paucity of high-quality randomised controlled trials or systematic reviews comparing SLTs to VHAs, for an evidence-based approach on this matter.

Ho et al. have also updated the current evidence on tranexamic acid, massive transfusion protocols (MTP) and goal-directed transfusion in this context. While the results of the randomised controlled trials (Prospective, Observational, Multicenter, Major Trauma Transfusion [PROMMTT] study and the Pragmatic, Randomized Optimal Platelet and Plasma Ratios [PROPPR] trial) were contrasting in terms of the survival outcomes, it needs to be accepted that a fixed ratio MTP may not be the ideal solution for the complex pathophysiology that coagulopathy of trauma entails.[9] It needs to be emphasised that goal-directed therapies based on coagulation tests (SLT or VHA) are gaining popularity in trauma resuscitation by virtue of its ability to cut down transfusion requirements, mortality and even healthcare costs. A stepwise sequential VHA algorithm might confer a higher predictive value for transfusion needs during trauma and there is a general trend that major trauma centres are embracing this paradigm shift. The role of early administration of fibrinogen in trauma is not yet clear. The availability of cryoprecipitate or fibrinogen concentrate at short notice might pose a challenge to effective implementation globally. However, we need to await the results of ongoing randomised controlled trials for evaluating the utility of fibrinogen concentrates in early trauma. In addition, although the review highlights early studies assessing the addition of 4-factor prothrombin complex concentrates that show a reversal of coagulopathy of trauma and reduction in transfusion requirements, this needs further evaluation before adoption into clinical practice.[10]

Overall, this narrative review emphasises the fact that coagulopathy of trauma needs early identification and prompt treatment. The authors have diligently compiled an evidence-based approach to the conundrum including a sequential algorithm. The proposed approach would be more meaningful if it is supplemented by a proper consensus definition of TIC among multidisciplinary specialists, similar to sepsis-induced coagulopathy, so that the yardstick to stratify and manage the problem remains universally accepted.[4] Current evidence supports the idea that TIC can be identified by SLTs or VHAs. The limitation of such tests performed in an ex vivo environment is that they do not adequately reflect the crosstalk between the endothelium, circulating platelets, clotting factors, local tissue and trauma-related inflammatory factors. Goal-directed therapy based on such tests is a step forward in reducing inappropriate transfusions when compared to fixed ratio MTP in this setting. Given that resources might vary across hospitals, a dynamic trauma resuscitation protocol that incorporates early MTP in the first hour and moves quickly on to a goal-directed transfusion strategy might be a more practical approach on the ground, so that resuscitation is not delayed in a massively bleeding trauma patient. Administration of tranexamic acid within 3 hours of trauma should be followed; however, its administration in the prehospital

setting needs to be looked into.[9] The use of fibrinogen concentrates in early trauma is an interesting concept while we await robust evidence from the randomised controlled trials. Eventually, once we close the knowledge gaps, the snapshot diagnostic assays and reactive management of coagulopathy of trauma should give way to a multivariate in silico modelling of the complex coagulation milieu.[1] This new future approach may be augmented by computational models and artificial intelligence that can predict dynamic phenotypes of TIC, allowing for more precise and optimal individualised treatment for trauma patients with bleeding.

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ORIGINAL ARTICLE

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The impact of deprescribing interventions on oral proton pump inhibitor utilisation in a Singapore tertiary hospital: A quality improvement initiative

Christina Jiun Yu Tan [1]*PharmD*, Shi Xun Lee [1]*BSc Hons (Pharm)*, Tat Ming Ng [1]*PharmD*

ABSTRACT

Introduction: Proton pump inhibitors (PPIs) are effective treatments for upper gastrointestinal pathologies and short-term courses are well-tolerated. However, indiscriminate use of PPIs is undesirable due to its potential harms. We implemented a series of deprescribing interventions between 2016 and 2017 to curb PPI overutilisation in our institution. The aim of this study was to evaluate the effectiveness and safety of these interventions.

Methods: An institutional PPI deprescribing guide was disseminated by email and educational roadshows were conducted to prescribers. Interrupted time series analysis was used to evaluate the effectiveness of the deprescribing interventions over a 7-year period from 2013 to 2019. To ascertain the safety of PPI deprescribing, we analysed the peptic ulcer disease incidence from 2015 to 2018 and conducted a retrospective chart review of 262 inpatients who were deprescribed PPIs.

Results: Following the first intervention, there was a significant decrease in mean oral PPI utilisation by 2,324.46 defined daily doses (DDD) per 1,000 prescriptions (95% confidence interval [CI] -3,542.66, -1,106.26) per month, followed by a month-to-month decrease of 302.61 DDD per 1,000 prescriptions per month thereafter (95% CI -473.95, -131.27). A second targeted educational intervention was only effective in sustaining the decline in the outpatient, but not in the inpatient setting. There were no significant changes in incidence of peptic ulcer disease. In the retrospective chart review, a majority (62.6%) of patients remained deprescribed at 6 months.

Conclusion: We observed a sustained decrease in PPI utilisation in our institution for more than 12 months following our educational interventions. Cautious deprescribing of PPIs in eligible candidates was found to be safe with low recurrence rates of upper gastrointestinal events.

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Keywords: Deprescribing, drug utilisation study, interrupted time series analysis, proton pump inhibitor, quality improvement initiative

INTRODUCTION

The established efficacy of proton pump inhibitors (PPIs) in the treatment of upper gastrointestinal (GI) disorders, coupled with their perceived safety, have led to PPI overutilisation.[1,2] Prescription of PPIs in absence of evidence-based indication, also known as low-value prescribing, is prevalent across the spectrum of healthcare settings.[1-4] Within Singapore, Chia et al. reported that approximately half of hospitalised inpatients were prescribed PPIs and 43.2% of these patients had no clear indications.[5] Anaemia (without evidence of GI bleeding), prophylaxis in low-risk aspirin/antiplatelet/non-steroidal anti-inflammatory drug users, and no apparent indication were the top 3 reasons for non-evidence-based PPI prescription.[5]

PPIs are not without ill effects. Mounting evidence suggests that excessive and prolonged PPI use is associated with increased risk of *Clostridium difficile* infection, pneumonia, fractures, hypomagnesaemia and chronic kidney disease.[6] Inappropriate or low-value PPI prescribing not only exposes patients to unnecessary adverse effects and drug interactions, it also increases pill burden and healthcare costs.[7]

Globally, there are many initiatives to guide PPI deprescribing.[8-10] Deprescribing is the "systematic process of identifying and discontinuing drugs when

[1] Department of Pharmacy, Tan Tock Seng Hospital, Singapore
Correspondence: Dr Christina Jiun Yu Tan, Department of Pharmacy, Tan Tock Seng Hospital, 11 Jalan Tan Tock Seng, Singapore 308433.
Email: christina_jy_tan@ttsh.com.sg

CLINICAL IMPACT

What is New

- To the best of our knowledge, this is the first study evaluating the long-term impact of proton pump inhibitor (PPI) deprescribing interventions in a tertiary hospital in Singapore.
- Interventions targeted at creating problem awareness, overcoming inertia to change and improving self-efficacy among clinicians contributed to a sustained reduction in PPI utilisation over 3 years without an increase in peptic ulcer disease incidence.

Clinical Implications

- Our findings support the safety of cautious PPI deprescribing, which will serve to reinforce clinicians' confidence to deprescribe PPIs in eligible patients.

existing or potential harms outweigh existing or potential benefits within the context of an individual patient's care goals, current level of functioning, life expectancy, values and preferences".[11] Specific to PPI, deprescribing entails dose reduction, switching to as-needed PPI use, stepping down to less potent acid-suppressant therapies (e.g. histamine-2 receptor antagonist (H2RA) or antacids), or discontinuation of therapy. In most deprescribing studies, reported success rate of deprescribing among patients with gastroesophageal reflux disease was 25–92%, with higher rates of success in dose reduction and as-needed PPI use than abrupt discontinuation.[12] Although there is a paucity of high-quality evidence on the cost-benefit of deprescribing PPIs, the benefit of reducing medication burden and its associated cost is a strong driver to reduce low-value PPI prescribing.

To curb the rising use of PPIs in our setting, we implemented a series of deprescribing interventions from 2016 to 2017. We then evaluated the impact of the interventions on PPI utilisation and the safety of deprescribing.

METHODS

Study setting and intervention

To reduce the rates of PPI overutilisation in Tan Tock Seng Hospital, we sequentially implemented a series of interventions that were broadly developed to target the themes identified by Anderson et al. in tackling inappropriate medications.[13] The first series of interventions targeted the themes of "problem awareness" and "self-efficacy". We developed an evidence-based PPI deprescribing guide, which was approved by our institution's clinical board. This guide was disseminated to physicians and pharmacists via email, and was made accessible at the point-of-care. We engaged the stakeholders through roadshows at selected prescribing medical (internal medicine, cardiology, general surgery and orthopaedic) and pharmacy departments. The content shared at these roadshows broadly included pre-intervention audit data, how to use the PPI deprescribing guide, highlight of common candidates for PPI deprescribing, and common reasons for inappropriate PPI prescription. We engaged pharmacists to proactively review continued indication of PPIs in their medication reviews and highlighted inappropriate PPI use suitable for deprescribing. These interventions (intervention 1) were implemented from October 2016 to January 2017.

PPI utilisation was reported to rebound back to baseline levels 12 months after implementation of a PPI deprescribing guideline in a long-term care home in Canada.[14] In view of this finding, we embarked on a second intervention 10 months after the first. This was a multidisciplinary initiative with physician representatives from internal medicine; geriatric medicine; gastroenterology and hepatology; and clinical pharmacists. Given that the impetus for clinicians to timely review continued prescription of PPIs was to refute the widespread misperception that PPIs are innocuous drugs, we designed and conducted an education session to internists within our institution in August 2017, using anonymised patient case studies to illustrate the potential harms associated with PPI use (intervention 2). This served to target the "inertia" theme defined by Anderson et al., as "the failure to act, despite awareness that prescribing is potentially inappropriate, because ceasing potentially inappropriate medications is perceived to be a lower value proposition than continuing".[13]

Evaluation

We examined the impact of our deprescribing interventions on 2 measures—PPI utilisation trends (for efficacy) over a 7-year period from 2013 to 2019, and incidence of peptic ulcer disease (PUD) (for safety) across a 4-year period from 2015 to 2018.

To evaluate the effectiveness of our deprescribing interventions, we conducted an interrupted time-series analysis (ITSA) of monthly PPI utilisation from January 2013 to December 2019 using pharmacy dispensing records. PPI utilisation was calculated using defined daily doses (DDD) of oral PPIs dispensed per 1,000 prescriptions in the outpatient care setting or on

discharge from an inpatient encounter in each month. We included all oral PPIs available in the formulary (omeprazole, esomeprazole, rabeprazole, lansoprazole and dexlansoprazole). Parenteral and oral PPI utilisation within an inpatient admission were excluded as our interventions were targeted at reducing prolonged low-value PPI prescription. For the safety analysis, an ITSA of incident PUD was performed over a 4-year period from January 2015 to December 2018. Incident PUD cases were identified using relevant International Classification of Diseases, Tenth Revision (ICD-10) codes (K25-28, as listed in either primary or secondary diagnoses) from the hospital database.

Additionally, to determine the safety of deprescribing in patients previously maintained on PPIs, we retrospectively reviewed medical records of inpatients identified to have oral PPIs deprescribed during their hospitalisation episode in the period from 1 June to 31 October 2017, when PPI utilisation was at its lowest, reflecting the peak of deprescribing efforts. Re-initiation/re-escalation of PPI doses within 6 months from discharge was used as the safety indicator. Hospitalised patients newly initiated on PPIs were likely to have PPIs continued on discharge; therefore, only patients who were taking PPIs prior to admission were included. Patients were excluded if there were incomplete post-discharge clinical data. Patients were followed up by chart review until oral PPIs was restarted, dose re-escalated, demise of the patient, or until the end of 6 months. Reasons for re-initiation/re-escalation of PPI doses, where available, were documented. Cause of death for patients who demised prior to PPI re-initiation/escalation was also documented if the information was available. Ethics approval was obtained from the NHG Domain Specific Review Board (DSRB 2017/00944).

Statistical analysis

For the efficacy analysis, ITSA models were constructed for overall, outpatient and inpatient PPI utilisation data, respectively, using Stata version 15 (StataCorp, College Station, US). The models were estimated using ordinary least squares regression where Newey-West regression was specified to account for an error structure that is assumed to be heteroskedastic and autocorrelated at lag 0.[15,16] The autocorrelation of each model was tested using Cumby-Huizinga test and visual inspection of autocorrelation and partial autocorrelation plots. Seasonality was examined using periodograms and cycle plots. In our models, no apparent seasonality was detected and was thus not reported. Non-stationarity was examined using Dickey-Fuller test with trend term included as there was a clear downward trend in monthly utilisation. Non-stationarity was not detected in all the charts.

For the safety analysis using PUD incidence data, a Poisson regression model was constructed as the outcome was count. Monthly count of PUD incidences per 1,000 patient-days were used as the outcome. To identify risk factors associated with upper GI bleeding events post-deprescribing in the retrospective chart review, data were analysed using chi-square test (or Fisher's Exact test where appropriate).

RESULTS

Effectiveness of deprescribing interventions

Between 1 January 2013 and 31 December 2019, a total of 5.08×10^7 DDD of oral PPIs were dispensed from our institution. Of this number, 19.5% were dispensed on discharge from an inpatient encounter. Mean PPIs dispensed at outpatient setting and inpatient discharge were 486,326 and 117,938 DDD per month, respectively. The mean number of prescriptions per month in outpatient and inpatient settings were 48,739 and 5,344, respectively.

Before intervention 1 (January 2013 to September 2016), overall month-to-month oral PPI utilisation decreased at an average rate of 78.84 DDD per 1,000 prescriptions per month (95% CI -105.17, -52.50) (Table 1). Immediately following the implementation of intervention 1 in October 2016, there was a significant drop in mean oral PPI utilisation by 2,324.46 DDD per 1,000 prescriptions (95% CI -3,542.66, -1,106.26) per month (level change), followed by a significant month-to-month decrease of 302.61 DDD per 1,000 prescriptions per month (95% CI -473.95, -131.27) thereafter (trend change) (Fig. 1A, Table 1). Overall mean oral PPI utilisation trend rebounded after intervention 2, with a non-significant increase of 557.41 DDD per 1,000 prescriptions (95% CI -592.25, 1707.06) per month and a significant month-to-month increase of 404.85 DDD per 1,000 prescriptions per month (95% CI 230.94, 578.77). Similarly, a significant month-to-month increase in mean oral PPI utilisation of 355.18 DDD per 1,000 prescriptions per month (95% CI 213.90, 496.46) was observed in the inpatient setting (Fig. 1C, Table 1).

In the outpatient setting (Fig. 1B, Table 1), following intervention 1, there was a significant decrease in mean oral PPI utilisation by 1,161.70 DDD per 1,000 prescriptions (95% CI -1,628.01, -695.39) per month, and a significant month-to-month decrease of 82.64

DDD per 1,000 prescriptions per month (95% CI -134.50, -30.78). The downward trend continued after intervention 2 at a more gradual rate, with a non-significant decrease in mean oral PPI utilisation of 167.31 DDD per 1,000 prescriptions (95% CI -510.58, 175.96) per month and a non-significant month-to-month increase of 49.67 DDD per 1,000 prescriptions per month (95% CI -2.92, 102.27).

By the end of the study period after both interventions, the overall oral PPI utilisation decreased by 1,930 DDD per 1,000 prescriptions per month when compared to the projected level based on the pre-intervention trend (Fig. 1). In the outpatient setting, PPI utilisation was 3,078 DDD per 1,000 prescriptions per month lower compared to that projected based on the pre-intervention trend. Conversely, in the inpatient setting, oral PPI utilisation increased from pre-intervention projected level by 1,148 DDD per 1,000 prescriptions per month. Based on a year-to-year comparison of annual PPI expenditure in year 2013 and 2019, the overall decline in PPI utilisation led to an estimated cost avoidance of SGD87,082 per annum.

Safety of deprescribing interventions

Time series analysis of incidence of PUD

Incidence of PUD as an unintended effect from decreased oral PPI utilisation was examined for any increase (Fig. 2, Table 2). There was no significant level or trend change in incidence rate ratio of PUD diagnosis before or after the 2 interventions.

Retrospective chart review of inpatients with PPI deprescribed

A total of 297 inpatients were identified to have PPI deprescribed prior to discharge from 1 June to 31 October 2017. Thirty-five patients were excluded due to incomplete records of post-discharge care, leaving 262 patients included for safety analysis. All patients were either on omeprazole or esomeprazole at baseline. Demographic characteristics of patients included are presented in Table 3.

The majority of patients were older adults ≥65 years (75.2%) and were taking >5 medications (72.1%). Most patients (75.2%) were on higher than standard doses of PPI at baseline. The most common method of deprescribing was dose decrease (51.9%), followed by complete discontinuation of acid-suppressant therapy (27.1%).

Outcomes of deprescribing are presented in Table 4. The majority of patients (62.6%) remained deprescribed at 6 months post-discharge. Twenty-three patients died;

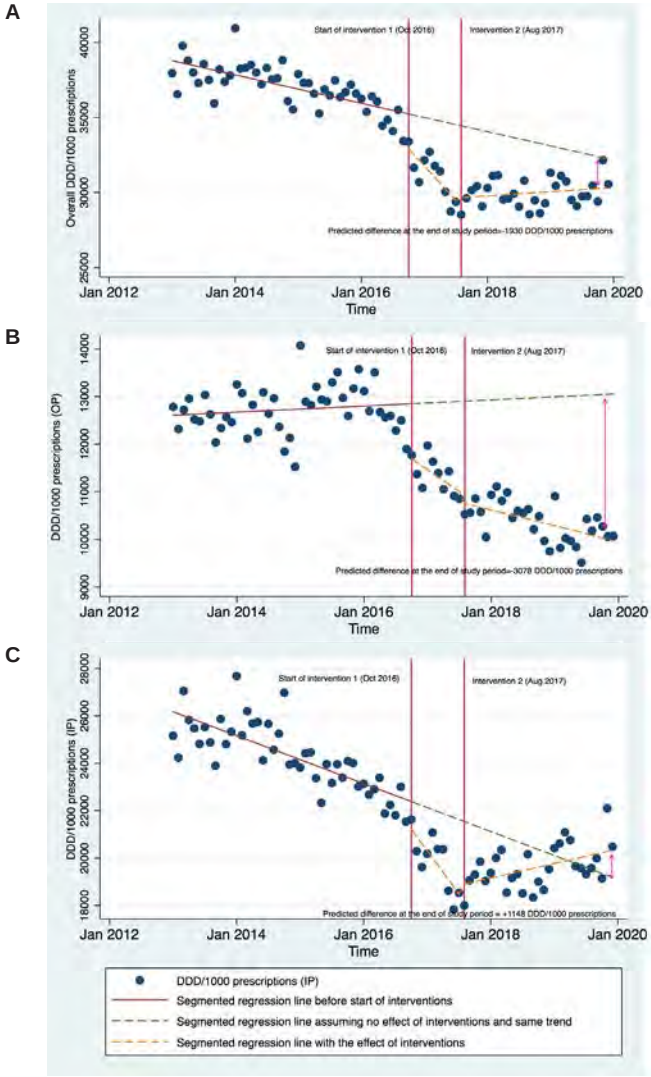

Fig. 1. Segmented regression models of proton pump inhibitor utilisation following intervention 1 and intervention 2. (A) Overall in the entire institution. (B) In outpatient (OP) setting. (C) In inpatient (IP) setting.
DDD: defined daily doses
[a] Intervention 1, initiated in October 2016, refers to a series of interventions comprising email dissemination of evidence-based proton pump inhibitor (PPI) deprescribing guide to physicians and pharmacists, roadshows to selected top prescribing departments, and active engagement of pharmacists to review continued indication for PPIs in hospitalised inpatients.
[b] Intervention 2, initiated in August 2017, comprised an education session to internists within our institution on the potential adverse consequences associated with PPI use.

information leading to the demise of 8 patients was not available. Among the remaining 15 patients, no death was attributed to upper GI events. Twenty-eight (10.7%) patients had PPIs escalated at follow-up with no documented reason; and 17 (6.5%) patients experienced an upper GI event warranting re-escalation of PPI therapy. Among the 9 (3.4%) patients who had clinical signs/symptoms or endoscopically diagnosed upper GI bleeding, deprescribing was assessed to be

Table 1. Interrupted time series analysis of the effect of interventions on monthly PPI use between January 2013 and December 2019

Baseline		**PPI utilisation, DDD per 1,000 prescriptions per month (95% CI)**	***P* value**	**Pre-intervention trend (95% CI)**	***P* value**
Prior to intervention, January 2013 to September 2016	Overall	38,784.91 (38,066.21, 39,503.62)	<0.01	-78.84 (-105.17, -52.50)	<0.01
	Outpatient	12,608.74 (12,386.20, 12,831.28)	<0.01	5.37 (-4.59, 15.34)	0.287
	Inpatient	26,176.18 (25,555.35, 26,797.01)	<0.01	-84.21 (-104.91, -63.51)	<0.01
Intervention		**Level change in PPI utilisation, DDD/1,000 prescriptions/month (95% CI)**	***P* value**	**Trend change after intervention (95% CI)**	***P* value**
Intervention 1, October 2016	Overall	-2,324.46 (-3,542.66, -1,106.26)	<0.01	-302.61 (-473.95, -131.27)	<0.01
	Outpatient	-1,161.70 (-1,628.01, -695.39)	<0.01	-82.64 (-134.50, -30.78)	<0.01
	Inpatient	-1,162.76 (-2,049.22, -276.29)	0.011	-219.97 (-357.98, -81.97)	<0.01
Intervention 2, August 2017 to December 2019	Overall	557.41 (-592.25, 1,707.06)	0.337	404.85 (230.94, 578.77)	<0.01
	Outpatient	-167.31 (-510.58, 175.96)	0.335	49.67 (-2.92, 102.27)	0.064
	Inpatient	724.71 (-307.57, 1,757.00)	0.166	355.18 (213.90, 496.46)	<0.01

CI: confidence interval; DDD: defined daily dose; PPI: proton pump inhibitor

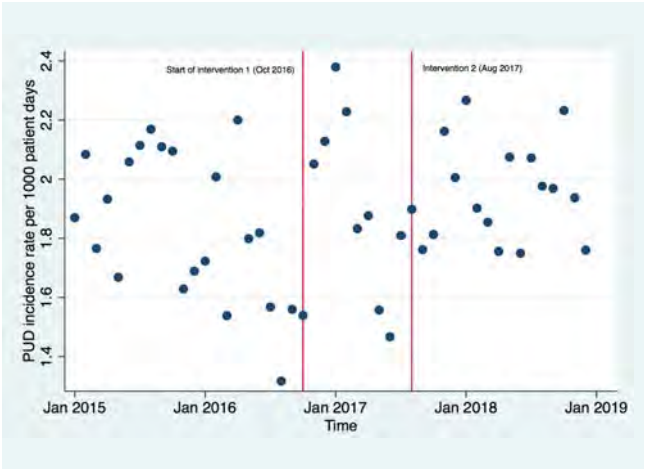

Fig. 2. Peptic ulcer disease incidence rate per 1,000 patient-days for the entire institution from 2015 to 2018.
PUD: peptic ulcer disease

reasonable based on a detailed review of the index inpatient encounter, except for 1 patient. This patient had a history of complicated PUD, was on concurrent aspirin and underwent deprescribing to a H2RA. For the remaining 8 patients, 4 had PPI discontinued, 2 had PPI doses reduced to 20mg, and 3 were de-escalated to H2RAs. Among the 4 patients whom PPI was discontinued, 2 had a history of complicated PUD more than 1 year ago. All 8 patients did not have clear evidence-based indication for chronic PPI use. Comparing patients who developed upper GI bleeding events with patients who remained deprescribed at the end of 6 months (n=173), there was no significant association of upper GI bleeding event with age ≥65 years, presence of chronic kidney disease or cirrhosis, known history of hiatal hernia, deprescribing method, uninvestigated anaemia, or use of either low-dose

Table 2. Parameter estimates, standard errors and *P* values from Poisson regression model of the incidence of peptic ulcer disease before and after intervention 1 and 2 within the entire institution

Baseline IRR (95% CI)	**Intervention 1**		**Intervention 2**	
	Level change (95% CI)	**Trend change (95% CI)**	**Level change (95% CI)**	**Trend change (95% CI)**
0.99 (0.94, 1.04)	1.26 (0.44, 3.63)	0.99 (0.84, 1.17)	1.15 (0.35, 3.80)	1.02 (0.86, 1.21)

CI: confidence interval; IRR: incidence rate ratio

Table 3. Characteristics of patients with proton pump inhibitors deprescribed during an inpatient encounter

Demographics	**N=262**
Age, mean (SD), years	73.0 (13.9)
Male sex, no. (%)	120 (45.8)
On chronic medications, no. (%)	
>5 medications	189 (72.1)
>10 medications	45 (17.2)
Baseline prescribed PPI dose, no. (%)	
≤20mg/day	65 (24.8)
40–60mg/day	157 (59.9)
80mg/day	40 (15.3)
Relevant comorbidities, no. (%)	
History of peptic ulcer disease	27 (10.3)
History of erosive oesophagitis	4 (1.5)
Previous/current GERD/dyspepsia	49 (18.7)
Hiatal hernia	21 (8.0)
Uninvestigated anaemia	29 (11.1)
History of suspected upper GI bleed	12 (4.6)
Has at least one of the comorbidities listed above	151 (57.6)
On treatment with at-risk drugs, no. (%)	
Aspirin	95 (36.3)
Non-aspirin antiplatelet	56 (21.4)
Anticoagulants	26 (9.9)
Steroids	18 (6.9)
COX-2 inhibitors	2 (0.8)
>1 at-risk drug	36 (13.7)
Deprescribing methods used, no. (%)	
Dose decreased	136 (51.9)
Discontinued	71 (27.1)
Stepped down to H2RA	49 (18.7)
Switched to on-demand PPI treatment	6 (2.3)

COX-2: cyclooxygenase-2; GERD: gastroesophageal reflux disease; GI: gastrointestinal; H2RA: histamine-2-receptor antagonist; PPI: proton pump inhibitor; SD: standard deviation

aspirin, non-ulcerogenic antiplatelet, anticoagulant, steroid or cyclooxygenase-2 inhibitor. Only patients with a documented history of PUD had a significantly higher rate of clinical/endoscopic GI bleeding events following deprescribing (3/17 [17.6%] versus 6/156 [3.8%], P=0.046).

Table 4. Outcomes of deprescribing

Outcomes of deprescribing	**No. of patients (%)**
PPI remained deprescribed at 6 months	164 (62.6)
Demise within 1st month	5 (1.9)
Demise within 6 months with no PPI reinitiated/ dose re-escalated	23 (8.8)
PPI reinitiated/dose re-escalated	75 (28.6)
Time point of re-initiation/dose re-escalation	
Within 1 month post-discharge	22 (8.4)
1–3 months post-discharge	28 (10.7)
>3–6 months post-discharge	25 (9.5)
Reasons for PPI re-initiation/dose re-escalation	
Escalated at follow-up with no documented reason	28 (10.7)
Anaemia/drop in Hb in absence of upper GI symptoms	10 (3.8)
Initiation of at-risk drug	8 (3.1)
Symptomatic dyspepsia/GERD	8 (3.1)
Clinical signs of upper GI bleed	5 (1.9)
Endoscopically diagnosed upper GI bleeding event	4 (1.5)
Clinical signs of lower GI bleed	2 (0.8)
Incidental finding of gastritis on oesophagogastroscopy	2 (0.8)
Helicobacter pylori treatment	1 (0.4)
Others	7 (2.7)

GERD: gastroesophageal reflux disease; GI: gastrointestinal; Hb: haemoglobin; PPI: proton pump inhibitor

DISCUSSION

Several studies have examined the impact of PPI deprescribing initiatives on PPI utilisation, but the studies did not examine unintended consequences.[14,17] The current study attempted to evaluate both the efficacy and safety of real-world deprescribing interventions implemented at a tertiary hospital. Our ITSA analysis showed that multifaceted, deprescribing educational interventions implemented in our institution was associated with a decline in overall oral PPI utilisation, without an increase in PUD incidence rate. The decline in outpatient oral PPI utilisation was sustained for 3 years post-intervention but a rebound in the inpatient setting was observed.

Prior to our first intervention, there was a gradual decline in oral PPI utilisation from 2014 to 2016. This may have been influenced by a preceding nationwide campaign kickstarted by the Pharmaceutical Society of Singapore during Pharmacy Week that was held from September to October 2015, which focused on PPIs as the prototype class of drugs to target deprescribing at a healthcare system level.[18] The observed impact was greater in the inpatient setting likely because the campaign was targeted mainly at pharmacists, and pharmacists are actively involved in daily medication reviews for all hospitalised patients. This contrasted with the outpatient setting where only a proportion of patients were referred for pharmacist-led medicine review services. Beyond our educational interventions, the observed reduction in PPI utilisation may have been contributed by a confluence of other factors such as environmental influence, supportive senior management, doctors' and pharmacists' involvement in driving rational prescribing within the institution, and increasing supportive literature over the years.[1,6,19]

Intervention 2 was less successful in preventing a rebound in oral PPI utilisation in the inpatient setting compared to outpatient. As the second intervention mainly engaged the internal medicine department, it was likely that interest may have waned in prescribers of other departments and among pharmacists, resulting in a subsequent rebound. Waning interest or failure to sustain deprescribing rate is not unexpected. Deprescribing is more often reactive, whereby discontinuation of a medication occurs when an adverse event happens. Proactive deprescribing entails identification of "potential harms" rather than "existing harms" and discontinuing therapy if the risks outweigh the benefits. The decision to deprescribe a medication is a continuous process requiring time, resources, rapport and communication between prescriber, pharmacist and patient.[20,21] Given that hospital admissions are frequently for acute issues, deprescribing often becomes less of a priority.[22,23] An alternative possibility of concern was whether the initial uptake in PPI deprescribing led to more inpatients requiring PPI therapy. However, this was unlikely as the PUD disease incidence remained stable across years 2014 to 2018. In addition, the retrospective chart review suggested that a majority (62.6%) of patients remained deprescribed at 6 months post-discharge.

Our retrospective chart review demonstrated a low rate of serious upper GI events in patients who were deprescribed. The majority of deprescribing was dose reduction or tapering, which tended to have higher success rates than abrupt discontinuation.[24] The association between history of PUD and occurrence of severe upper GI event suggested that PPI should be deprescribed with caution in these patients. A significant proportion of patients with PPI re-initiated/dose re-escalated (37.3%) at post-discharge follow-up had no documented reasons, reflecting possible fragmentation of care due to incomplete transfer of information on medication changes at the transition of care. This might have undermined our deprescribing efforts.

A major limitation of our study was that the appropriateness of PPI prescription was not analysed. Overall PPI utilisation data, normalised against the number of prescriptions, were used as a surrogate marker to evaluate the impact of our quality improvement interventions. Our ITSA had assumed that the observed pre-intervention trend would continue into the future using a regression model. However, it did not take into account a basal utilisation rate of evidence-based PPI prescription, which was estimated at 56.8% of baseline based on previously published point-prevalence data among hospitalised inpatients in Singapore.[5] Additionally, without the inclusion of a control group, the association observed in our ITSA was not conclusive of the impact of interventions implemented.

ICD-10 codes for PUD incidence were used as a balance measure to identify signals of potential harm associated with our PPI deprescribing efforts. We recognised that the method was limited by the accuracy of ICD-10 coding, as well as the inability to identify patients with PUD who presented to other healthcare institutions, or to the primary care setting. Hence, we complemented the safety analysis with a chart review of patients who were taking regular PPI pre-admission and had PPI deprescribed by discharge. This inclusion criterion may have missed patients who were initiated and deprescribed PPI within the same admission. Furthermore, as the patient sample for the chart review spanned the second intervention, it may have inevitably introduced some bias.

Our findings from a single tertiary care centre have limited generalisability to primary care settings. Nevertheless, it may support the use of educational interventions targeted at common perceived barriers to drug deprescribing. Further work is required to identify strategies that are sustainable in the long-term. Deprescribing should ideally be proactive and conducted by a multidisciplinary team with emphasis on patient communication, shared decision-making and intervention sustainability.[25]

CONCLUSION

Educational interventions targeted at deprescribing PPIs were associated with a decrease in PPI utilisation at the institution level, which sustained for more than 12 months. Cautious deprescribing of PPIs in eligible candidates was found to be safe with low recurrence rates of upper GI events.

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ORIGINAL ARTICLE

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Novel transdermal device for delivery of triamcinolone for nail psoriasis treatment

Yik Weng Yew *[1,2]*MBBS*, Crystal Zhen Yu Phuan *[1]*MRCP*, Xiahong Zhao [1]*PhD*, Eugene Sern Ting Tan [1]*MBBS (Singapore)*, Wei-Sheng Chong [1]*FAMS (Dermatology)*, Hong Liang Tey [1,2,3]*FAMS (Dermatology)*

ABSTRACT

Introduction: Nail psoriasis treatment is challenging due to difficult drug delivery and systemic therapy toxicities. Self-dissolvable microneedle patches embedded with corticosteroids offers a potentially rapid, minimally invasive drug delivery platform with good efficacy and minimal adverse side effects.

Methods: We conducted a 4-month prospective randomised controlled trial. Subjects with psoriatic nails were randomised to receive microneedle device delivered topical steroids on one hand and control treatment (topical Daivobet gel) on the other. Two independent dermatologists blinded to the treatment assignment scored their Nail Psoriasis Severity Index (NAPSI) during visits at baseline, 2 and 4 months. All treatment was discontinued after 2 months. Average NAPSI score on each hand was analysed.

Results: A total of 25 participants were recruited, aged 22 to 73 years. Majority were Chinese (72%), followed by Indian and Malay. There was equal randomisation of treatment to the left and right nail. While there was a rapid significant improvement in average NAPSI score for the control arm at 2 months, the treatment arm had a greater, more sustained improvement of the NAPSI score at 4 months. The average NAPSI score improved for both treatment and control group at 4 months compared to baseline. However, only the NAPSI value improvement in the controls at 2 months compared to baseline was statistically significant (P=0.0039). No severe adverse effects were reported.

Conclusion: To the best of our knowledge, this is the first prospective randomised control trial comparing microneedle technology against conventional topical steroids in nail psoriasis treatment. Our findings demonstrate microneedle technology is as efficacious as topical therapy.

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Keywords: Microneedle, nail, psoriasis

INTRODUCTION

Psoriasis is a chronic immune mediated inflammatory skin condition that affects about 2–4% of the Western populations, with rising incidence over the years.[1,2] The presentation of psoriasis varies from mild localised plaques to more severe erythrodermic forms, with plaque-type psoriasis being the most common. It frequently affects the skin and scalp, with up to one-third of patients with joint involvement[3] and over half with nail psoriasis.[4] Classical psoriatic nail lesions include nail plate pitting, onycholysis, nail bed discolouration, subungual hyperkeratosis and onychodystrophy. Pitting is the most common sign, followed by onycholysis;[5] but this may not be specific and can be seen in a variety of other nail conditions. The lifetime prevalence of nail involvement for psoriasis patients is estimated to be 80–90%[4] and this may present in the absence of cutaneous or joint disease in 5–10% of patients.[6] It is likely that the prevalence of nail psoriasis may be underestimated[7] and commonly overlooked as it is largely asymptomatic in the early stage, especially when patients experience more symptoms from their skin and joint involvement. However, early recognition is important for early intervention as nail psoriasis is considered an indicator for future or early psoriatic joint damage,[8] and can

[1] National Skin Centre, Singapore
[2] Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore
[3] Yong Loo Lin School of Medicine, National University of Singapore, Singapore
* Joint first authors
Correspondence: Dr Hong Liang Tey, National Skin Centre, Dermatology, Singapore 1 Mandalay Road, Singapore 308205.
Email: hltey@nsc.com.sg

CLINICAL IMPACT

What is New

- Microneedle patches are as effective as conventional topical steroid treatment at 4 months to serve as additional or alternative treatment for nail psoriasis.

Clinical Implications

- Self-application of our novel microneedle patches may improve delivery of care and healthcare outcomes for patients compared to intralesional triamcinolone injections that require physician administration and clinic visits.

be associated with longer disease duration, greater disease severity, and greater restrictions in activities of daily living. This can result in lower quality of life as measured with validated instruments such as Dermatology Life Quality Index (DLQI) and Nail Psoriasis Quality of life 10 (NPQ10).[9,10]

Routine evaluation and early treatment of nail involvement in psoriasis patients is therefore important. Patients should be evaluated in a holistic manner for severity of nail changes, as well as extent of skin and joint involvement. Nail psoriasis is known to be difficult to treat; current treatment modalities include topical therapy, intralesional therapy, photochemotherapy, laser therapy, radiotherapy and systemic therapy, including the use of biologics. Most importantly, patient education on general nail care measures is essential as some patients turn to manicuring practices such as artificial nails and nail extensions to conceal dystrophy, which may in turn irritate nails[11] and worsen their overall condition.

While topical therapy is a good initial option for patients with proximal nail matrix disease manifesting as pitting of the nails, it has limited efficacy for nail bed disease with subungual hyperkeratosis as topical therapy has suboptimal nail bed access. Beyond topical treatments, procedural therapies such as pulsed dye laser and intralesional corticosteroids have been investigated as possible treatment options. Monthly pulse dye laser therapy has limited efficacy, with long duration of treatment required.[12] Intralesional injection of corticosteroids can have moderate efficacy but requires in-person weekly injections by a physician for months.[13] The treatment is very painful, precluding its routine use. Further treatment options such as oral systemic and biologic therapies have been found to be effective but the potential associated adverse side effects limit their use to patients with concurrent more severe cutaneous involvement.[14] Patients are often fatigued, due to poor efficacy of various treatment modalities and failure to comply to long-term treatments with topical agents. The treatment of nail psoriasis remains challenging due to great difficulty in drug delivery to site of action and possible toxicities of most conventional systemic therapies. With the advent of a new transdermal drug delivery platform in the form of microneedle technology,[15] the option of a rapid and painless drug delivery to the nail matrix is promising. To investigate the therapeutic effects and advantages of using microneedle technology to deliver topical corticosteroids to psoriatic nails in a rapid and painless way, we conducted a prospective, randomised controlled study to compare microneedle technology with current conventional topical steroid treatment in the treatment of nail psoriasis.

METHODS

We conducted a 4-month prospective randomised controlled trial in National Skin Centre, a tertiary dermatology centre in Singapore to evaluate treatment response of nail psoriasis following treatment with a self-dissolving microneedle drug delivery patch to administer topical steroids to psoriatic nails. We included all adult patients, aged 21 years and above, with nail psoriasis affecting both hands in varying severity, diagnosed by certified dermatologists. All patients recruited also had classical chronic plaque psoriasis diagnosed by dermatologists. There was consideration of alternative differentials for 2 of the patients. However, their fungal nail microscopy and culture performed were negative, suggesting that the diagnosis of onychomycosis was unlikely. The study excluded those with unilateral nail psoriasis present on one hand had previous localised phototherapy to their nails, oral systemic agents, biologics or have a history of allergy to alcohol swabs, steroids or hyaluronic acid. Patients with recent topical treatment of nails or who were undergoing whole body narrow band ultraviolet B therapy were included but were advised to maintain symmetrical positioning during treatment. All patients underwent a fingernail clipping for microscopy to rule out onychomycosis before enrolment in the study.

This was a left to right intrapatient comparison trial where study participants received sterile microneedle topical steroids treatment on 1 hand and control treatment (topical Daivobet gel containing 50µg/g calcipotriol and 500µg/g betamethasone, as dipropionate) on the other hand. Randomisation was performed for each participant to determine treatment allocation for 2 hands. This was done with a computer-generated sequence by a dedicated person who had no further

involvement in the rest of the study. Patients were taught by research assistants on the way to administer the treatment patch and control treatment.

These dissolving microneedle patches (Fig. 1) were made of sodium hyaluronate as water-soluble matrix material with a total of 0.5mg triamcinolone embedded in the distal 50% of the microneedles. The microneedles are 600μm in length and pyramidal in shape. They are prepared via a micromould-based method with a stainless steel master structure consisting of 225 pyramidal needles created using an electrical discharge machining process. The total amount of triamcinolone (0.5mg) in each microneedle patch to be applied twice weekly was calculated based on the weekly dosage of up to a maximum of 0.1mL of 10mg/mL injected to proximal nail folds in reported literature.[16] Alcohol swabs were provided to wipe the nail fold prior to application. The microneedle patches were being held in place over the nail fold area with a nail patch applicator clip (Figs. 2 and 3).

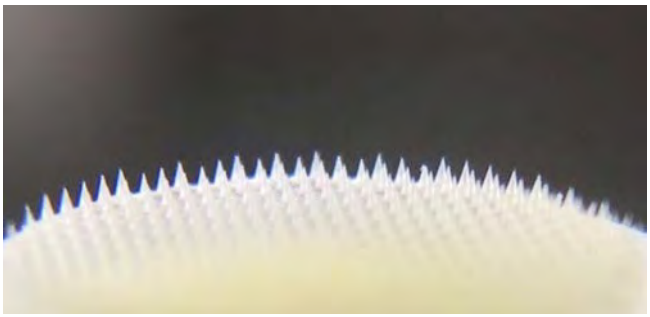

Fig. 1. Microneedle self-dissolving patch.

To assess the severity of psoriatic nail disease, Nail Psoriasis Severity Index (NAPSI) was used in our study. Being one of the most comprehensive assessment tools of psoriatic nail disease used in clinical trials,[17] it has been validated as a numeric, reproducible, objective and simple tool for evaluation of treatment response of psoriatic nails. In this system, the nail is divided into 4 quadrants and 1 point is awarded if there is any finding of nail matrix and 1 for nail bed change that is seen, per quadrant, or 0–8 per nail. Nail matrix psoriasis was assessed by the presence of any feature of nail matrix psoriasis, including nail pitting, leukonychia, red spots in the lunula, and crumbling in each quadrant of the nail. Nail bed psoriasis was assessed by the presence of features such as onycholysis, oil drop (salmon patch) dyschromia, splinter haemorrhages, and nail bed hyperkeratosis in each quadrant of the nail. NAPSI scoring was administered by 2 independent

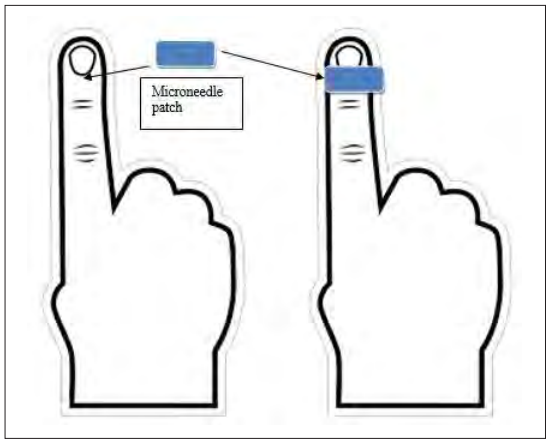

Fig. 2. Application of microneedle patch over horizontal nail fold.

Fig. 3. Clinical photograph of application of nail patch applicator clip.

dermatologists blinded to the treatment assignment at baseline and follow-up visits (2-month and 4-month visits). The average NAPSI nail score of the affected nails on each hand was analysed. This was calculated from the total NAPSI nail score of psoriasis-affected nails divided by the number of affected nails. Other clinical information such as Psoriasis Area Severity Index (PASI), Dermatology Life Quality Index (DLQI) and NPQ10 were measured at baseline and follow-up visits. All recruited patients were reviewed at baseline and at 2 and 4 months after treatment initiation. All treatment was discontinued after 2 months. The study concluded after the third visit (4 months) and all patient information was collated. Any localised side effects to the fingers were also recorded during the follow-up visits.

In previous studies,[18,19] patients recruited at baseline from a population with psoriatic nails had a mean NAPSI nail score of about 6 with a standard deviation of 2. Based on the assumption that patients recruited for our study will have similar baseline scores for both the case and control groups, we expect a 1–1.5 point score difference in nail changes between active and control groups after 4 months of treatment at the end of the study. Based on these assumptions, a sample size of 16–34 is required to detect 1–1.5 point score difference in nail changes between the 2 groups with statistical power of 80%, at 5% significance level. Hence, a sample size of 20 patients was decided to achieve the above statistical power at 5% significance level. The primary outcome of this study was NAPSI scores, and secondary outcomes were PASI, DLQI and NPQ10 scores, all measured at the 2-month and 4-month follow-up visits. Differences between the active against control group, as well as differences between study visits within each treatment group were reported in medians with ranges and means with standard deviations (SD). Wilcoxon signed-rank test was used to compare differences. Statistical significance was assessed at a level of 0.05. All statistical analysis were performed using R version 3.5.3 software. The above study design and methods were approved the Singapore institute ethics board prior to initiation.

RESULTS

A total of 25 patients were recruited for the study, and their demographic characteristics were shown in Table 1. They were aged 22 to 73 years with most of them being males (76.0%). Majority of the patients were Chinese (72%), followed by Indians (3%) and Malays (3%). There was approximately equal randomisation of treatment to the left (48%) and right nail (52%). Four study participants did not complete the third study visit as they were either lost to follow-up or could not complete their follow-up due to COVID-19 visit restrictions.

There was a rapid significant improvement in average NAPSI score for the control arm at 2 months, while the treatment arm with microneedles had a more sustained and greater improvement of the NAPSI score at 4 months (Fig. 4). The average NAPSI score improved for both the treatment and the control arm in the third visit compared to the first visit, but only the improvement of the NAPSI value in the control group at 2 months compared to baseline was statistically significant (P=0.004) (Table 2). The control group showed higher improvement at 2 months compared with the treatment group but the improvements at 4 months for both groups were similar (Table 3). These findings reflect that treatment with microneedle patches are at least as effective as the conventional topical steroid treatment. In addition, more than half of patients (52%) indicated a score of at least 7 when asked to rate their willingness to use the microneedle patch if it was available in the market on a scale of 0 to 10. All patients were monitored for adverse events (AE) with only 1 patient with missing AE data. Of the 9 (37.5%) patients who reported AE, 7 reported pain, 1 reported discomfort with the clip, 1 reported peeling skin and 1 reported numbness. Of the 7 patients who reported pain, none reported a pain score exceeding 2 out of 10. The Koebner phenomenon was not observed at the nail folds where microneedles were applied. The overall psoriasis severity remained similar throughout the 4-month study period with similar PASI scores for all 3 visits. However, it was noted that there was a significant decrease in DLQI scores from baseline to 2 months as the study participants received localised therapies targeted to their nails. (Table 4).

Table 1. Demographics of study participants

Characteristics	**n=25**
Age, years	
Median (range)	43 (22–73)
Mean (SD)	43.28 (14.44)
Sex, no. (%)	
Male	19 (76.0%)
Female	6 (24.0)
Race, no. (%)	
Chinese	18 (72.0)
Malay	3 (12.0)
Indian	3 (12.0)
Others	1 (4.0)
Randomisation, no. (%)	
Treatment: Left nail	12 (48.0)
Treatment: Right nail	13 (52.0)

SD: standard deviation

DISCUSSION

Nail psoriasis is prevalent in both psoriasis and psoriatic arthropathy. There is recent increased emphasis on treatment as nail psoriasis is increasingly recognised to have negative impacts on the quality of life and ability

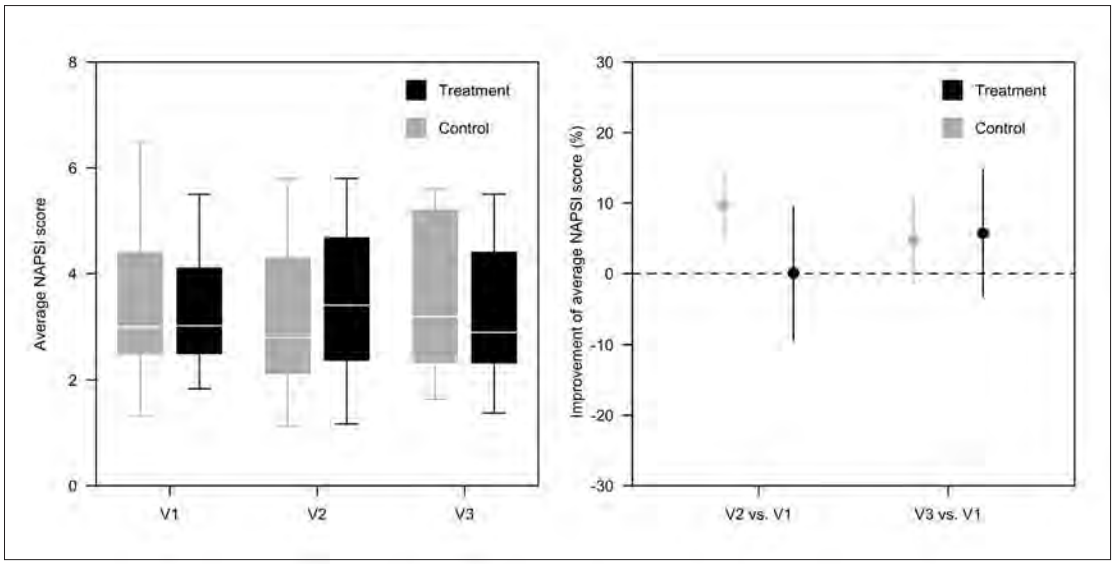

Fig. 4. Comparison of average Nail Psoriasis Severity Index (NAPSI) scores between treatment and control arms across baseline (V1) and follow-up visits (V2 and V3).
V: visit

to perform daily activities. With limitations to current therapy methods due to poor penetration,[20] tedious administration and side effects, microneedle technology for drug delivery has come into focus. This is especially relevant in psoriasis, where keratinocyte hyperproliferation causes the formation of prominent plaques that further hinders transdermal delivery. Microneedles can potentially serve as a method of drug delivery considered superior to conventional transdermal delivery as it is known to be minimally invasive, painless, convenient and promotes improved patient compliance.[21] So far, the use of microneedles has been tested with the administration of methotrexate,[22,23] cyclosporin[24,25] and biologics[26,27] such as anti-TNF-alpha antibody, with good results and minimal side effects. The use of a hyaluronic acid-based microneedle patch had previously been examined in a pilot open trial to treat psoriatic plaques with promising results, but evidence on microneedle patches to treat psoriatic nails is lacking.[28]

Our findings demonstrate that treatment with microneedle patches were at least as effective as conventional topical steroid treatment. The conventional topical steroids treatment had demonstrated a rapid better treatment response compared to the microneedle treatment. While the observed higher NAPSI score at visit 2 for treatment arm was not statistically significant (Table 2), the significantly better improvement scores at visit 2 for control group compared to treatment group could be attributed to a possible delay in any treatment effects from the microneedle compared to the control treatment. Nevertheless, any visible treatment effects seem to be similar between the 2 treatment arms after 4 months, suggesting that the microneedle treatment might have a slower onset or the effects could

Table 2. Average NAPSI score within each group across baseline (V1) and follow-up visits (V2 and V3)

	V1 (n=5)	**V2 (n=5)**	**V3 (n=21)**	***P* value (V2 vs V1)**	***P* value (V3 vs V1)**
Treatment					
Median (range)	3.02 (1.83–5.5)	3.4 (1.17–5.8)	2.9 (1.38–5.5)	0.90	0.06
Mean (SD)	3.42 (1.19)	3.42 (1.39)	3.31 (1.39)		
Control					
Median (range)	3 (1.32–6.5)	2.8 (1.12–5.8)	3.2 (1.63–5.6)	0.004	0.10
Mean (SD)	3.54 (1.45)	3.22 (1.41)	3.53 (1.39)		

NAPSI: Nail Psoriasis Severity Index; SD: standard deviation; V: visit

Table 3. Percentage improvement of NAPSI scores at follow-up visits (V2 and V3) from baseline (V1)

	V1 (n=25) %	V2 (n=25) %	V3 (n=21) %
Treatment			
Median (range)	3.02 (1.83–5.5)	-2.5 (-37.5–50)	6.38 (-58.18–41.32)
Mean (SD)	3.42 (1.19)	0.07 (24.34)	21; 5.71 (21.26)
Control			
Median (range)	3 (1.32–6.5)	9.3 (-16.67–37.5)	3.45 (-28–36.8)
Mean (SD)	3.54 (1.45)	9.68 (12.84)	21; 4.73 (14.72)
P value	0.13	0.02	0.84

NAPSI: Nail Psoriasis Severity Index; SD: standard deviation

Table 4. Quality of life markers: PASI, DLQI, NPQ10 across baseline (V1) and follow-up visits (V2 and V3)

	V1	V2	V3	*P* value (V2 vs V1)	*P* value (V3 vs V1)
PASI	n=24	n=23	n=20		
Median (range)	1.65 (0–20.1)	1 (0–10.7)	1.9 (0–17.4)	0.26	0.58
Mean (SD)	2.86 (4.60)	2.23 (3.02)	2.92 (4.18)		
DLQI	N=25	N=24	N=20		
Median (rrange)	4 (0–24)	2 (0–19)	3.5 (0–27)	0.02	0.33
Mean (SD)	6.16 (5.75)	4.25 (5.02)	6.10 (7.52)		
NPQ10	n=25	n=24	n=19		
Median (range)	0 (0–14)	0 (0–14)	0 (0–15)	0.86	0.89
Mean (SD)	1.40 (2.96)	1.54 (2.98)	1.84 (3.58)		

DLQI: Dermatology Life Quality Index; NPQ10: Nail Psoriasis Quality of life 10; PASI: Psoriasis Area Severity Index; SD: standard deviation

possibly be more persistent.

Various matrix materials have been utilised in previous studies to examine the efficacy of drug delivery. Our study used hyaluronic acid as the matrix material for the microneedles in view of its excellent biological properties of biodegradability and non-immunogenicity. The self-dissolvable hyaluronic acid microneedle patch loaded with corticosteroids provides enhanced drug delivery to the nails. These microneedle patches have micron-scale needles that can permeabilise the stratum corneum by creating microchannels in the skin, thereby allowing the embedded corticosteroids to penetrate the nail matrix and bed. These microneedles are long enough to pierce through the barrier but short enough to avoid causing pain. We observed that the treatment arm with microneedles had a more sustained and greater improvement of the NAPSI score at 4 months, but this was not statistically significant. This might be related to the need for a larger sample size or a longer duration of follow-up for the clinical trial.

A strength of this study is its intrapatient design where each patient served as his own case and control for treatment response, which reduces the possible confounders to treatment response. In addition, patients with recent prior treatment with systemic effects were excluded. Our study demonstrates that microneedle patches have the potential to serve as an important adjunct treatment option for nail psoriasis, an alternative to topical therapy, and even intralesional triamcinolone injections. With the potential for self-application of microneedle patches at home, patients have the convenience of home therapy. This will be ideal for patients with busy schedules who are not able to make regular clinic visits for triamcinolone injections. There

will also be potential time and cost savings as patients need not make multiple clinic visits. Delivery of care to patients and their healthcare outcomes are also likely to improve. Most patients reported no adverse outcomes from applying the nail microneedles and most adverse effects were limited to during the application process. In addition, better designed or customised nail fold applicators could be considered for improved fitting and less discomfort for application.

One of the main limitations of this study is the lack of long-term follow-up, as it is possible that nail dystrophy can relapse just like psoriasis. Furthermore, given the natural speed of nails growth, there might be a lag in any visible nail improvement. Since all treatment was concluded in 2 months but followed up for 4 months, this limited duration might have limited the efficacy of each treatment. Conversely, possible longer-term side effects of microneedle use not observed in this study include infection, irritant contact dermatitis, allergic contact dermatitis, post-inflammatory hyperpigmentation, abnormal scarring, and irritant and allergic granulomas.[29] A longer duration of treatment and follow-up could show more promising results with the microneedle patch. Further studies with a larger sample size could be performed by expanding on this pilot trial to detect smaller treatment differences with adequate statistical power.

CONCLUSION

To the best of our knowledge, this is the first prospective randomised control trial comparing the efficacy of microneedle technology against current conventional topical steroid treatment in the treatment of nail psoriasis. While new biologic therapies effective for both plaque psoriasis and psoriatic arthritis are promising for the treatment of nail psoriasis, topical treatments should still be the first-line therapy especially in individuals who have predominantly nail psoriasis with limited systemic involvement. Further research with larger sample sizes is required to further support the use of microneedles to fill treatment gaps in terms of optimal dose adjustments and application frequency, as part of clinical management of nail psoriasis and for further development in this drug delivery field.

Disclosure

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REVIEW ARTICLE

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Academy of Medicine, Singapore clinical guideline on the use of sedation by non-anaesthesiologists during gastrointestinal endoscopy in the hospital setting

Tiing Leong Ang [1]*FAMS*, Edwin Seet [2]*FAMS*, Yaw Chong Goh [3]*FAMS*, Wee Khoon Ng [4]*FAMS*, Calvin Jianyi Koh [5]*FAMS*, Hock Foong Lui [6]*FAMS*, James Weiquan Li [1]*FAMS*, Aung Myint Oo [7]*FAMS*, Kieron Boon Leng Lim [3]*FAMS*, Kok Sun Ho [3]*FAMS*, Min Hoe Chew [8]*FAMS*, Wai Leong Quan [9]*FAMS*, Damien Meng Yew Tan [10]*FAMS*, Kheng Hong Ng [6]*FAMS*, Hak Su Goh [6]*FAMS*, Wai Kit Cheong [11]*FAMS*, Philip Tseng [3]*FAMS*, Khoon Lin Ling [3]*FAMS*

ABSTRACT

Introduction: In Singapore, non-anaesthesiologists generally administer sedation during gastrointestinal endoscopy. The drugs used for sedation in hospital endoscopy centres now include propofol in addition to benzodiazepines and opiates. The requirements for peri-procedural monitoring and discharge protocols have also evolved. There is a need to develop an evidence-based clinical guideline on the safe and effective use of sedation by non-anaesthesiologists during gastrointestinal endoscopy in the hospital setting.

Methods: The Academy of Medicine, Singapore appointed an expert workgroup comprising 18 gastroenterologists, general surgeons and anaesthesiologists to develop guidelines on the use of sedation during gastrointestinal endoscopy. The workgroup formulated clinical questions related to different aspects of endoscopic sedation, conducted a relevant literature search, adopted Grading of Recommendations, Assessment, Development and Evaluation (GRADE) methodology and developed recommendations by consensus using a modified Delphi process.

Results: The workgroup made 16 recommendations encompassing 7 areas: (1) purpose of sedation, benefits and disadvantages of sedation during gastrointestinal endoscopy; (2) pre-procedural assessment, preparation and consent taking for sedation; (3) Efficacy and safety of drugs used in sedation; (4) the role of anaesthesiologist-administered sedation during gastrointestinal endoscopy; (5) performance of sedation; (6) post-sedation care and discharge after sedation; and (7) training in sedation for gastrointestinal endoscopy for non-anaesthesiologists.

Conclusion: These recommendations serve to guide clinical practice during sedation for gastrointestinal endoscopy by non-anaesthesiologists in the hospital setting.

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Keywords: Benzodiazepines, gastrointestinal endoscopy opiates, propofol, sedation

[1] Department of Gastroenterology and Hepatology, Changi General Hospital, Singapore
[2] Department of Anaesthesia, Khoo Teck Puat Hospital, Singapore; Department of Anaesthesia, National University of Singapore
[3] Mount Elizabeth Medical Centre, Singapore
[4] Department of Gastroenterology and Hepatology, Tan Tock Seng Hospital, Singapore
[5] Department of Gastroenterology and Hepatology, National University Hospital, Singapore
[6] Gleneagles Medical Centre, Singapore
[7] Department of General Surgery, Tan Tock Seng Hospital, Singapore
[8] Department of General Surgery, Sengkang General Hospital, Singapore
[9] Royal Square Medical Centre, Singapore
[10] Department of Gastroenterology and Hepatology, Singapore General Hospital, Singapore
[11] Department of Surgery, National University Hospital, Singapore
Correspondence:
Dr Khoon Lin Ling, Mount Elizabeth Medical Centre, 3 Mount Elizabeth, Singapore 228510.
Email: drlingkl@gmail.com
Prof Tiing Leong Ang, Department of Gastroenterology and Hepatology, Changi General Hospital, 2 Simei Street 3, Singapore 529889.
Email: ang.tiing.leong@singhealth.com.sg

CLINICAL IMPACT

What is New

- This is the first Academy of Medicine, Singapore evidence-based guideline on the use of sedation during gastrointestinal endoscopy by non-anaesthesiologists, developed using Grading of Recommendations, Assessment, Development and Evaluation (GRADE) methodology.
- The guideline addresses the use of propofol for sedation by non-anaesthesiologists in the hospital setting.
- It highlights the importance of structured training for the safe and effective use of sedation.

Clinical Implications

- This guideline will enhance the safety and quality of sedation during gastrointestinal endoscopy by non-anaesthesiologists in the hospital setting.

INTRODUCTION

The practice of gastrointestinal (GI) endoscopy over the last 3 decades has seen both a rise in volume of routine procedures, and an increase in the breadth and complexity of procedures. Routine endoscopies have increased due to a growth in population size, and also due to the introduction of guidelines for the routine surveillance of malignant and pre-malignant lesions of the colon and the upper GI tract. There has also been a surge in the number of new complex endoscopic procedures. These more complex procedures last longer and may require patients to be well sedated. The expectations of patient populations have also changed. While gastroscopy and colonoscopy began as unsedated procedures, some patients now expect to be well sedated for routine diagnostic gastroscopy and colonoscopy.

The practice of GI endoscopy and sedation varies between different countries. In Singapore, both gastroenterologists and surgeons perform GI endoscopy. Endoscopic procedures are performed in either standalone ambulatory centres or endoscopy suites located within hospital premises. Internationally, the proportion of patients undergoing endoscopy who are sedated by endoscopists and by anaesthesiologists have increased. In the US, about 50% of patients are now sedated by anaesthesiologists.[1] Currently in Singapore, endoscopic sedation is often administered by the endoscopist because of considerations such as the established track record of safety and convenience, anaesthesiology manpower constraints and additional costs associated with anaesthesiologist-administered sedation. Patients are assessed before endoscopy and those needing anaesthesiologist-administered sedation will receive that level of care. For the others, the endoscopist has been safely delivering sedation. The drugs used for sedation during GI endoscopy in hospital endoscopy centres now include propofol—in addition to benzodiazepines and opiates—unlike standalone ambulatory centres, which do not use propofol without anaesthesiologist support. The requirements for peri-procedural monitoring and discharge protocols have evolved. There is a need to develop an evidence-based clinical guideline on the safe and effective use of sedation by non-anaesthesiologists during GI endoscopy in Singapore in the hospital setting. While a guideline on the use of sedation by non-anaesthesiologists for medical and dental clinics, standalone ambulatory surgical centres and standalone endoscopy suites in Singapore has been published by the Ministry of Health (last updated in July 2021),[2] it does not address the issues pertinent to the hospital setting. This guideline bears no reference to the guideline for standalone endoscopy suites.[2] It focuses specifically on the use of sedation by non-anaesthesiologists for all GI endoscopy procedures performed within the hospital setting in adult patients. There is an extensive body of evidence for the safety and efficacy of various drugs in GI endoscopy sedation. There is also a difference between hospital-based practice and non-hospital-based practice.

METHODS

The Academy of Medicine, Singapore (AMS) appointed an expert workgroup led by 2 co-chairs to develop a guideline on the use of sedation during GI endoscopy. (See Supplementary Materials for Appendix 1 in online version of this article.) The group comprising 9 gastroenterologists, 7 general surgeons and 2 anaesthesiologists who were fellows of AMS, involved both public and private sector stakeholders. The workgroup was divided into sections to examine clinical questions (CQ) for different aspects of endoscopic sedation (Table 1). Literature search specific to each CQ was performed by the individual sections. Table S1 (Appendix 2 in online Supplementary Materials) provides literature search terms. PubMed database was searched for original articles, meta-analyses and guidelines related to the practice of GI endoscopy and sedation use, focusing on the efficacy and safety of different types of sedation (benzodiazepines, opiates and propofol), personnel administering the sedation, as well as sedation monitoring. Meta-analyses

and randomised trials were prioritised over observational studies. The references of guidelines previously published by academic societies were also reviewed for additional relevant literature. The search period was up to 31 March 2021. Each section generated an initial set of statements. Grading of Recommendations, Assessment, Development and Evaluation (GRADE) methodology was used to evaluate the quality of evidence and assess the strength of recommendations (Table 2).[3] These statements were collated and edited by the co-chairmen before circulation to the entire workgroup for the first round of voting, comments and modification.

The formal consensus procedure used the modified Delphi technique. The first round of voting was conducted electronically. For each statement, members were asked to vote on whether to "accept completely", "accept with some reservations", "accept with major reservations", "reject with some reservations" or "reject completely". The statements were modified based on the comments received. The modified statements were discussed and voted on in a second round of voting during an in-person meeting on 10 April 2021 at the Academy of Medicine, Singapore. The voting process with contributions of content and voting results were documented. A statement was accepted if 80% or more of the group voted to "accept completely" or "accept with some reservations". The explanatory text for each statement was drafted by the workgroup members of the section responsible for the specific CQ. The 2 co-chairs compiled and edited the full manuscript, which was then circulated to all workgroup members for vetting. The completed guideline was formally circulated by email for review by the governing Council of AMS and it was endorsed by the AMS Council without further amendment. Feedback through email was sought from Ministry of Health, Singapore and minor amendments were made to the manuscript explanatory text to provide greater clarity of its purpose and applicability. The statements are summarised in Table 3.

Table 1. Clinical questions

1.	Purpose of sedation, benefits and disadvantages of sedation during gastrointestinal (GI) endoscopy
2.	Pre-procedural assessment, preparation and consent-taking for sedation
3.	Efficacy and safety of drugs used in GI endoscopy sedation
4.	The role of anaesthesiologist-administered sedation during GI endoscopy
5.	Intraprocedure monitoring of sedated patient
6.	Post-sedation care and discharge after sedation
7.	Training in sedation for GI endoscopy for non-anaesthesiologist

Table 2. Grading of Recommendations Assessment, Development and Evaluation (GRADE)

Quality of evidence
• **High:** Consistent evidence from well-performed randomised, controlled trials or overwhelming evidence of some other form. Further research is unlikely to change our confidence in the estimate of benefit and risk.
• **Moderate:** Evidence from randomised, controlled trials with important limitations (inconsistent results, methodologic flaws, indirect or imprecise), or very strong evidence of some other research design. Further research (if performed) is likely to have an impact on our confidence in the estimate of benefit and risk and may change the estimate.
• **Low:** Evidence from observational studies, unsystematic clinical experience, or from randomised, controlled trials with serious flaws. Any estimate of effect is uncertain.
Strength of recommendation
• **Strong recommendation:** When it is very certain that benefits outweigh risks and burdens (such as difficulties of therapy and costs), or vice versa.
• **Weak recommendation:** When risks and burdens appear to be finely balanced, or when there is appreciable uncertainty about the magnitude of benefits and risks.

RESULTS

CQ1: Purpose of sedation, benefits and disadvantages of sedation during GI endoscopy

Statement 1: Sedation should be offered to every patient undergoing endoscopy. Specific informed consent should be taken for procedural sedation after the risks and benefits have been discussed with the patient.

Quality of evidence: Moderate

Strength of recommendation: Strong

Agreement: 94.4%

Procedural sedation, besides the direct benefit of reducing procedural discomfort,[4] has also been shown to reduce patient anxiety and results in greater willingness to repeat the procedure.[5] From the perspective of the endoscopist, there is also evidence of sedation improving endoscopy quality. For example, a recent single-centre review of outpatient colonoscopies demonstrated sedation to be associated with improved caecal intubation rates and adenoma detection rates.[6]

An important part of patient autonomy involves ensuring that patients give consent to procedural sedation. This allows the patient to make voluntary decision on their medical care after having understood the attendant benefits and risks of sedation. Consent for procedural moderate sedation should be taken by an individual familiar with the sedation process. Procedural sedation may be administered by a non-anaesthesiologist or an anaesthesiologist. When medically relevant or when practicable, this option will be discussed with the patient.

Table 3. Summary of statements

	Statements	Quality of evidence	Strength of recommendation	Final vote
Purpose of sedation, benefits and disadvantages of sedation during gastrointestinal (GI) endoscopy Pre-procedural assessment, preparation and consent-taking for sedation				
1	Sedation should be offered to every patient undergoing endoscopy. Specific informed consent should be taken for procedural sedation after the risks and benefits have been discussed with the patient.	Moderate	Strong	94.4%
2	Unsedated endoscopy is possible in selected patients. We recommend that where unsedated endoscopy is planned, options should be discussed ahead should the patient not be able to tolerate an unsedated procedure.	Moderate	Strong	100%
3	Patients undergoing sedation should be assessed medically for risks of sedation.	Low	Strong	100%
Efficacy and safety of drugs used in GI endoscopy sedation				
4	A benzodiazepine alone or in combination with an opioid is an option for sedation for patients undergoing diagnostic and therapeutic gastrointestinal endoscopy.	High	Strong	100%
5	Propofol alone or in combination with a benzodiazepine or opioid is an option for sedation for patients undergoing diagnostic and therapeutic gastrointestinal endoscopy.	High	Strong	100%
The role of anaesthesiologist-administered sedation during GI endoscopy				
6	Propofol sedation for gastrointestinal endoscopy can be safely and effectively administered by trained non-anaesthesiologists.	High	**Weak**	94.4%
7	We recommend anaesthesiologist-administered sedation in patients with a high-risk profile.	Low	Strong	100%
Intraprocedure monitoring of sedated patient				
8	A dedicated and trained assistant for sedation monitoring should be available during the procedure.	Low	Strong	94.4%
9	An individual trained in airway management and resuscitation should be on-site or immediately available.	Low	Strong	100%
10	Continuous oximetry monitoring is recommended for gastrointestinal endoscopy monitoring.	Low	Strong	100%
Post-sedation care and discharge after sedation				
11	We recommend that the patient's clinical parameters should be monitored after endoscopy by trained staff until fit for discharge.	Low	Strong	100%
12	We recommend the usage of a discharge scoring system, e.g. Post-Anaesthetic Discharge Scoring System (PADSS) or Modified Aldrete Score, to assess if patient has recovered sufficiently post-sedation to allow discharge.	Low	Strong	100%
13	We recommend that patients who have received sedation should be told what is safe for them to do.	Low	Strong	100%
Training in sedation for GI endoscopy for non-anaesthesiologist				
14	The person providing sedation should attend a sedation course.	Low	Strong	100%
15	Training in sedation should be structured. There should be assessment of competencies prior to the independent administration of sedation.	Low	Strong	100%
16	Non-anaesthesiologists using propofol for sedation should have additional training with respect to propofol. They should have training for resuscitation with emphasis on airway management.	Low	Strong	88.9%

The components of appropriate informed consent for procedural sedation include the following:

1. Specific informed consent must be obtained prior to procedural sedation. Ideally, this should be in documented consent, and not just oral or implied consent.
2. The sedation consent is either taken personally by the sedationist, or another healthcare provider in the context of team-based practice. There should be appropriate training and education of all healthcare providers taking sedation consent.
3. Informed consent should be carried out by trained and competent staff in a manner and language the patient can understand. If there are language difficulties, interpreters must be used.
4. The identity of the individual providing the information to the patient and family is to be documented in the medical records.
5. The purpose, risks, benefits and alternatives relating to procedural sedation are to be discussed with the patient, or with those who make decisions for the patient such as his or her family.
6. The patient may withdraw or modify his or her consent at any time.
7. The clinician must ensure that the patient understands the information given regarding sedation consent.
8. Major complications and risks of procedural sedation should be communicated to the patient.

Statement 2: Unsedated endoscopy is possible in selected patients. We recommend that where unsedated endoscopy is planned, options should be discussed ahead should the patient not be able to tolerate an unsedated procedure.

Quality of evidence: Moderate

Strength of recommendation: Strong

Agreement: 100%

Sedation during endoscopy may improve rate of complete endoscopies, the quality of endoscopic examination and outcomes of therapeutic endoscopy.[4,6] However, there are instances where sedation is not required or is not desired by the patient. These include procedures that are relatively short and less stimulating, e.g. flexible sigmoidoscopy[7] or water-insufflation colonoscopy.[8,9] Patients in whom sedation poses an increased risk, such as patients with severe obstructive sleep apnoea, may also choose to undergo endoscopy unsedated. In patients where unsedated endoscopy has been planned, it is reasonable to discuss options should the patient not be able to tolerate the procedure unsedated. These options include the administration of sedation by the endoscopist (for which pre-procedure assessment should be performed and consent taken), or cancellation and rescheduling of the procedure with anaesthesiologist support where appropriate.

CQ2: Pre-procedural assessment, preparation and consent taking for sedation

Statement 3: Patients undergoing sedation should be assessed medically for risks of sedation.

Quality of evidence: Low

Strength of recommendation: Strong

Agreement: 100%

Pre-procedure assessment should be done to determine whether an anaesthesiologist should be involved during the sedation for the endoscopy.[10-12] This includes taking history and reviewing the medical records, performing a focused physical examination, and reviewing available investigations (Table 4 provides an example of such a schema).

CQ3: Efficacy and safety of drugs used in GI endoscopy sedation

Statement 4: A benzodiazepine alone or in combination with an opioid is an option for sedation for patients undergoing diagnostic and therapeutic gastrointestinal endoscopy.

Quality of evidence: High

Strength of recommendation: Strong

Agreement: 100%

Adequate comfort improves the safety and quality of digestive endoscopy.[6,13,14] Nearly all gastroscopies in the US and Australia are done with sedation and greater than 98% of the colonoscopies done in the US, Australia and Canada involve the use of sedation.[15] Although sedation practices vary from country to country, among the drugs used most commonly for GI endoscopy are opioids and benzodiazepines.

A benzodiazepine is typically used to minimise anxiety and to provide sedation during digestive endoscopy.[12] Its amnesic property helps in persuading patients for repeat procedures when indicated. An opioid, on the other hand, provides both sedative and analgesic effects and improves the quality of endoscopy. The combination of a benzodiazepine and opioid has been accepted and adopted by endoscopists worldwide as a regimen for

Table 4. Pre-procedure assessment for sedation

1. History
   a. Significant past medical history such as cardiopulmonary disorders
   b. Stridor, snoring or obstructive sleep apnoea
   c. Adverse reaction to sedation or anaesthesia
   d. Current medications and allergies
   e. Alcohol use
   f. American Society of Anesthesiologists (ASA) physical status classification
      i. ASA I, ASA II patients and some ASA III patients are appropriate candidates for administration of sedation by an endoscopist.
      ii. The assistance of an anaesthesiologist should be considered for some ASA III and all ASA IV, V patients.
2. Physical examination
   a. Vital signs and weight
   b. Auscultation of heart and lungs
   c. Baseline level of consciousness
   d. Assessment of airway
      • The airway evaluation is designed to identify patients with anatomy that may make emergency tracheal intubation during resuscitation more difficult. This includes patients with obesity, short thick neck, cervical spine disease, decreased hyoid-mental distance, decreased thyromental distance, short inter-incisor distance and structural abnormalities of the mouth, jaw and oral cavity, and higher Mallampati score. Anaesthesiologist referral and support may need to be considered in patients with such airway abnormalities undergoing sedation.
3. Investigation
   a. Blood test: not routinely indicated
   b. Electrocardiogram: not routinely indicated
   c. Chest X-ray: not routinely indicated

providing moderate sedation for routine GI endoscopy.[16,17] Although this approach carries a small risk of adverse events including hypotension, hypoxia, cardiac arrhythmia and apnoea, these risks have largely been mitigated with active pre-procedure case selection, intraprocedure and post-procedure monitoring.[18] The overall cost-benefit effect after risk balancing is in favour of such sedation regime in both inpatient and outpatient settings provided there are no added risk factors for sedation related adverse events.

Statement 5: Propofol alone or in combination with a benzodiazepine or opioid is an option for sedation for patients undergoing diagnostic and therapeutic gastrointestinal endoscopy.

Quality of evidence: High

Strength of recommendation: Strong

Agreement: 100%

Efficacy and safety of propofol

Propofol sedation is efficacious and has advantages over benzodiazepines and other sedatives for GI endoscopy, in terms of peri-procedural amnesia effect, faster recovery profile, patient satisfaction and endoscopist satisfaction. Propofol is more effective and safer than benzodiazepine in diagnostic and therapeutic endoscopy in patients with certain comorbidities such as liver cirrhosis.[19] Propofol sedation is efficacious and is equivalent to benzodiazepines for GI endoscopy in terms of peri-procedural haemodynamic changes and oxygenation. There is abundant medical literature in the form of randomised control trials[19-63] as well as meta-analyses/systematic reviews[5,64-72] comparing the use of propofol with benzodiazepines during GI endoscopy. Most studies were published from the year 2000 onwards with the majority concentrated in the last 10 years. The studies originated from centres with different healthcare systems from across the world, involving both adult and paediatric endoscopic procedures. The studies included diagnostic gastroscopy and colonoscopy, balloon-assisted enteroscopy, endoscopic ultrasound (EUS), and therapeutic procedures such as oesophageal band ligation, endoscopic mucosal resection and endoscopic retrograde cholangiopancreatography (ERCP). The studies assessed metrics related to patient cardiorespiratory parameters (oxygen saturation, heart rate and blood pressure) and related adverse events (hypoxaemia, bradycardia, hypotension and necessity of airway intervention), technical performance of endoscopy (e.g. caecal intubation and time to completion), recovery time, patient's satisfaction and endoscopist's satisfaction. A significant finding was that propofol was associated with faster recovery time after endoscopy. There was also improved patient satisfaction and endoscopist satisfaction with the use propofol. Meta-analyses noted that propofol sedation produced deeper sedation than traditional agents.[5,64-72] However, there

was no difference in complications in respect to cardiorespiratory parameters, with the exception of 1 meta-analysis noting a higher incidence of hypotension in propofol sedation.[64] One meta-analysis noted lower cardiorespiratory complications (blood pressure, oxygen saturation and heart rate) in the group sedated with propofol for colonoscopy but there were no differences in complications for other endoscopic procedures.[69] Propofol was also associated with a significantly faster recovery time. Both patients' and endoscopists' satisfaction was better with propofol than traditional agents. The confidence intervals in the meta-analyses were not wide.

In the 45 randomised control trials, propofol was compared with other sedation agents such as midazolam, fentanyl and etomidate.[19-63] Propofol was either given as monotherapy or in combination with one of these agents. Salient findings are as listed: propofol results in faster recovery time; propofol gives better quality upper GI endoscopy; propofol used in cirrhotic patients results in much less issues with hepatic encephalopathy post-sedation;[19,23] the adverse events were similar whether propofol was used or added to traditional agents; and etomidate is a promising alternative to propofol.

Propofol monotherapy versus combination therapy

Monotherapy propofol sedation has a low sedation-related complication rate. A recent large (n=368,206) multicentre German study recorded a 0.01% rate for major complication, where propofol monosedation had the lowest rate (odds ratio 0.75) compared with midazolam (reference) and combinations (odds ratio 1.0–1.5).[73] In a randomised controlled trial of 150 elderly patients 80 years or older presenting for routine ERCP, propofol as a single sedation agent was superior to midazolam and pethidine in terms of patient cooperation, recovery times and recovery score; with comparable intraprocedural desaturation.[74] In contrast, a randomised controlled trial (n=135) comparing propofol versus propofol and midazolam for colonoscopy sedation by non-anaesthesiologists showed that drug synergy in the combination group improved patient satisfaction rates but prolonged recovery time.[39] A dose-ranging study with propofol and increasing doses of fentanyl (up to 1µg/kg) in elderly colonoscopy patients (n=90) demonstrated that propofol dose can be reduced with combination therapy without significant difference in anaesthesia associated adverse events.[75] Similarly, safe and effective sedation for colonoscopy (n=121) with low-dose propofol together with dexmedetomidine or intranasal sufentanil or pethidine, can be achieved in different regimens.[76] Combination sedation regimens with preprocedural oral midazolam 7.5mg and propofol showed a propofol-sparing effect with less procedural anxiety and intraprocedural desaturation versus propofol monotherapy.[77] Large observational studies have demonstrated that propofol monotherapy has lower complication rates. However, several randomised controlled trials have shown that combination sedation can also be safely and effectively administered. Therefore, the evidence to support propofol monotherapy over propofol combination therapy is conflicting and the recommendation is weak. The experience of the endoscopist/sedationist utilising different regimens would be an important consideration for the use of combination therapy, vis-à-vis propofol with midazolam, dexmedetomine, fentanyl, pethidine or other anxiolytic or analgesic agents.

Statement 6: Propofol sedation for gastrointestinal endoscopy can be safely and effectively administered by trained non-anaesthesiologists.

Quality of evidence: High

Strength of recommendation: Weak

Agreement: 94.4%

On the question of the safety of non-anaesthesiologist-administered propofol for sedation during endoscopy, 2 areas were investigated, namely comparison of non-anaesthesiologist-administered versus anaesthesiologist-administered propofol for sedation in endoscopy and comparison of non-anaesthesiologist-administered propofol versus benzodiazepine. Three meta-analyses showed that the incidence of complications such as hypoxia and requirements for airway intervention during endoscopy were similar in both the non-anaesthesiologist-administered and anaesthesiologist-administered propofol groups.[78-80] Bradycardia was more common in the non-anaesthesiologist group. The non-anaesthesiologist group administered lower doses of propofol.

In the 2 randomised control trials directly comparing non-anaesthesiologist-administered versus anaesthesiologist-administered propofol, restricted to low-risk patients (American Society of Anesthesiologists [ASA] I–II), there were no differences between the 2 groups in complication rates (hypoxaemia, airway intervention, hypotension and bradycardia), technical success of endoscopy, as well as patient and endoscopist satisfaction.[81,82] In 3 large case series, 2 studies showed anaesthesiologist-administered sedation resulted in higher rates of serious adverse effects events and did not provide a safety benefit over non-anaesthesiologist-directed sedation, as well as higher rate of colonoscopy complications.[83,84] The third and smallest case series

concluded equal effectiveness of both non-anaesthesiologist-administered propofol and anaesthesiologist-administered propofol.[85] A small single-centre study by Goudra et al. showed that "the frequencies of most adverse events were significantly higher in patients anaesthetised with propofol".[86] This study compared adverse events when patients were sedated with propofol by anaesthesiologists or anaesthesiology nurses compared with non-propofol-based sedation by endoscopists. These conclusions have to be taken in the context of the limitations of case series studies where inherent bias may be present. In the randomised control trials comparing non-anaesthesiologist-administered sedation using propofol compared with benzodiazepine-based regimes, there was uniformity and concordance; there was no difference in safety and complication rates between the 2 groups.[39,45,87-89]

These studies comprising meta-analyses, randomised control trials and non-randomised studies point to safety of non-anaesthesiologist-administered propofol for sedation in endoscopy, in particular when compared to anaesthesiologist-administered propofol sedation, and compared to non-propofol, benzodiazepine-based regimens. We note that propofol was associated with a shorter recovery time, although it has a narrow therapeutic range and no reversal agent, with a tendency for progression from moderate to deep sedation.

The current product insert by the manufacturer states that propofol should be administered by "persons trained in the administration of general anaesthesia". Published evidence shows the efficacy and safety of non-anaesthesiologist-administered propofol for endoscopy compared with anaesthesiologist-administered propofol sedation. The product insert does not take into account post-marketing extensive evidence on the safety of propofol in the real-world setting, and propofol sedation is already currently been administered by non-anaesthesiologists. It is because of this evidence that it was felt necessary to have separate guidelines for sedation in GI endoscopy to create a framework for safe practice. The resources required to enable this parity in safety and efficacy should be noted. Specifically, the availability of clinical protocols, training requirements of non-anaesthesiologists, availability of personnel trained in airway management, and the manpower onsite. In the absence of a funnel plot, we also cannot rule out publication bias from the meta-analyses.[78-80] Dossa et al. performed a systemic review of the recommendations from published North American and European guidelines on sedation practices for routine GI endoscopy, and found that recommendations relating to the drugs to be used for sedation, the healthcare personnel capable of administering propofol and monitoring patients sedated with propofol, and the need for capnography when monitoring sedated patients varied.[90] There are controversies and limitations of available data and recommendations. We find that the level of evidence for this proposed recommendation statement moderate to high, with a weak recommendation due to possible publication bias, indirectness and the imprecision of the studies. The critical issue for endoscopic procedures is not the administration of propofol by an anaesthesiologist versus an endoscopist, but rather the monitoring of the patient to detect complications, the ability of the physician to recognise and manage the complications, and the availability of resources to manage these complications.

CQ4: The role of anaesthesiologist administered sedation during gastrointestinal endoscopy

Statement 7: We recommend anaesthesiologist-administered sedation in patients with a high-risk profile.

Quality of evidence: Low

Strength of recommendation: Strong

Agreement: 100%

A high-risk profile includes critically ill and/or decompensated patients (ASA IV–V); some ASA III patients; the presence of pathological anatomical features associated with a higher risk of airway obstruction during the intervention; history of obstructive sleep apnoea; obese patients with BMI>35kg/m^2; anticipated difficult airway; anticipated or history of intolerance to moderate sedation; patients with high risk of aspiration, prolonged or complex therapeutic endoscopic procedures requiring deep sedation; and anticipated difficulty in sedating patient.

The need for anaesthesiologist-administered sedation can be divided into patient and procedural factors. Patient factors include patients with a high-risk profile;[11,91] patients with anatomic or post-therapy airway variants predisposing to airway obstruction; patients with anticipated intolerance to standard sedatives, e.g. a history of alcohol or substance abuse; pregnancy; morbid obesity; neurologic or neuromuscular disorders; severe obstructive sleep apnoea; and patients who are uncooperative or delirious. The endoscopist may want to consider anaesthesiologist-administered sedation in geriatric patients and patients with BMI>30kg/m^2.

Procedural factors include prolonged or therapeutic procedures requiring deep sedation.[11]

In keeping with patient autonomy, the endoscopist may also consider anaesthesiologist-administered sedation in patients who have requested for an anaesthesiologist.

CQ5: Intraprocedure monitoring of the sedated patient

Statement 8: A dedicated and trained assistant for sedation monitoring should be available during the procedure.

Quality of evidence: Low

Strength of recommendation: Strong

Agreement: 94.4%

Monitoring of a patient under sedation serves the following purposes:

1. Gauge the level of sedation reached. This allows titration of the drugs used.
2. Observe and evaluate physiologic functions and extent of changes.
4. Early detection of unintended depth of sedation.
5. Evaluate patient's responses to intervention.

It is recommended that a dedicated and trained assistant, who could be a nurse or physician, be assigned to monitor the sedated patient and should have no other major duty.[92-99] Such individuals would have been trained to recognise and react to abnormalities in the parameters being monitored. While the assistant may provide momentary non-technical assistance to the other staff engaged in the technical part of the endoscopy, attention on the patient must not be diverted by these tasks.

Statement 9: An individual trained in airway management and resuscitation should be on-site or immediately available.

Quality of evidence: Low

Strength of recommendation: Strong

Agreement: 100%

A sedated patient is at risk of hypoventilation, obstruction, apnoea or losing the airway, which leads to hypercapnia and hypoxaemia.[9,21] Often ventilatory support would stabilise the patient.[73] In the hospital setting, an emergency response team (e.g. code blue team) with personnel proficient in airway management and cardiac resuscitation should be available at all time of the day. In the absence of this team, the endoscopist and/or endoscopy nurse should be trained and competent in airway management and resuscitation. Airway management equipment must be readily available.

Statement 10: Continuous oximetry monitoring is recommended for gastrointestinal endoscopy monitoring.

Quality of evidence: Low

Strength of recommendation: Strong

Agreement: 100%

The use of oximetry is currently ubiquitous in clinical practice, because of its easy non-invasive application, low cost and negligible risk. Observational studies have shown the utility of oximetry when procedural sedation is administered for endoscopy.[100-102] Timely intervention is enhanced with the use of oximetry monitoring in endoscopy units, which in turn improves patient safety.[103] In contrast, Bilotta et al. monitored oximetry in 103 patients undergoing office colonoscopy. As there were no adverse outcomes noted in this small patient group, the authors suggested that oximetry monitoring may not be clinically useful in low-risk endoscopies.[104]

Other monitoring devices

The group considered the evidence for the routine use of capnography and continuous electrocardiogram for intraprocedural monitoring but decided against making statements on their use as there was variation in actual clinical practice, differences in opinion about the necessity, and we did not consider these to be crucial in all cases.

CQ6: Post-sedation care and discharge after sedation

Statement 11: We recommend that the patient's clinical parameters should be monitored after endoscopy by trained staff until fit for discharge.

Quality of evidence: Low

Strength of recommendation: Strong

Agreement: 100%

In general, evidence on post-sedation care and discharge after endoscopic procedures is limited. Post-sedation complications (commonly hypoxia, hypotension or stridor) may happen after completion of the procedure. This usually happens within 30 minutes from the final sedative administration or in patients who have received reversal agents during or after the procedure.[105] Therefore, clear documentation of the sedative administration timing and usage of reversal agents is essential. Patients who have received sedation need to be closely monitored post-procedure by trained staff who can recognise and manage any common complications early. These complications are observed to be less

frequent when patients received propofol monotherapy, compared to the combination of benzodiazepines and opioids.[74]

Statement 12: We recommend the usage of a discharge scoring system, e.g. Post-Anaesthetic Discharge Scoring System (PADSS) or Modified Aldrete Score, to assess if patient has recovered sufficiently post-sedation to allow discharge.

Quality of evidence: Low

Strength of recommendation: Strong

Agreement: 100%

There are several discharge scoring systems available. The commonly used scoring systems are Post-Anaesthetic Discharge Scoring System (PADSS) and Modified Aldrete Score, which use the combination of vital signs, functional status and symptoms to allow trained staff to objectively assess if patients can be safely discharged after receiving sedation. Usage of these scoring systems may also allow earlier discharge, with no additional adverse outcome, compared to conventional clinical assessment.[106-109] These scoring systems, however, do not measure a patient's psychomotor or cognitive function and do not assess one's ability to drive or to make legally binding decisions. If reversal agents such as flumazenil or naloxone are used, one would need to ensure that sufficient time be allowed for the effects of these reversal agents to wear off, to avoid the situation of apparent fulfilment of discharge criteria, only for the patient to return to a sedated state which may endanger the patient or others after the reversal agents wear off.

Statement 13: We recommend that patients who have received sedation should be told what is safe for them to do.

Quality of evidence: Low

Strength of recommendation: Strong

Agreement: 100%

Discharge scoring systems often focus on only the cardio-respiratory function.[12,106-110] Despite patients appearing clinically alert post-reversal agents, they may have prolonged impairment in their cognition and psychomotor skills. The duration of this impairment depends on the sedative agent used.[111] These simple discharge scoring systems often do not assess patients' psychomotor function fully, which is important to determine if the patients are able to make use of road transport, operate heavy machinery or make legally binding decisions.

They should refrain from driving, drinking alcohol, operating heavy machinery, or engaging in legally binding decisions for a period of time, taking into account the half-life of the drug used and the patient's health profile. Advice should be provided verbally and in written form to the patient. Older studies on the recovery of psychomotor function after sedation with diazepam and midazolam showed recovery of psychomotor function to pre-sedation levels after 10 hours even when benzodiazepines were used at higher doses (midazolam 0.15mg/kg body weight [bw] or diazepam 0.45mg/kg bw).[112,113] Diazepam is seldom used in endoscopy now. The dose of midazolam administered also rarely exceeds 0.1mg/kg bw in current practice. Only when pethidine 75mg was used were psychomotor functions impaired for up to 12 hours.[114] This dose of pethidine is now seldom used during endoscopy. More recent studies have shown that patients sedated with propofol monotherapy recover psychomotor skills 2 hours post-sedation.[115,116] Patients in both studies had similar results on the driving simulator 2 hours after sedation. Japanese patients had similar number connection test (NCT) results before and 2 hours after propofol sedation while German patients took 1 second longer to complete the NCT. German patients who were sedated with midazolam and an opioid however scored worse on both the NCT and the driving simulator 2 hours post-sedation. American and Japanese experience suggests patients sedated with drugs with a short half-life may be safely discharged without an accompanying person,[117,118] and that they may drive home safely within a few hours of sedation.[117] Patients who have received sedation should be discharged with a responsible person and avoid operating heavy machinery, driving or signing any legally binding documents for a period. Based on current evidence on the duration of psychomotor function impairment by the drugs currently in use, patients given midazolam and fentanyl should be discharged with a responsible person and avoid these activities for up to 12 hours. Patients given propofol monotherapy could potentially avoid these activities for a shorter period. Published data would suggest it is safe for such activity to resume 2 hours after sedation.[115-117] However, given medico-legal considerations, it will be prudent for individual endoscopy units and endoscopists to discuss the implications of this with individual patients before sedation is given.

CQ7: Training in sedation for GI endoscopy for non-anaesthesiologist

Statement 14: The person providing sedation should attend a sedation course.

Quality of evidence: Low

Strength of recommendation: Strong

Agreement: 100%

Training and achieving competency in the use of medications, as well as in airway assessment and management is important. Drugs widely used in endoscopy sedation include benzodiazepines and opioids, such as midazolam and fentanyl, respectively.[119-122] Optimal sedation in endoscopy requires the proceduralist or seditionist administering sedation to be aware of the drugs' different pharmacokinetics, pharmacodynamics, route of elimination, common adverse effects and potential drug–drug interactions.[121,123-125] This enables the proceduralist or sedationist to choose the appropriate type, combination, and dose of sedation to administer depending on the patient profile, dosing aliquot interval, monitoring, and available and clinical setting. Adequate training in the properties of reversal agents such as flumazenil and naloxone are necessary in case these agents are required.[126,127] The continuum from complete consciousness to general anaesthesia does not progress in discrete and well-defined stages. As such, it is crucial that the proceduralist or sedationist who intends to administer sedation be trained in the assessment of the patient's level of sedation.[128,129] It is also important that the endoscopist or sedationist should be able to assess a patient's suitability for endoscopist directed sedation. This should include classifying patients' general health status using the ASA classification system[15] and a detailed airway evaluation including body habitus, cervical spine movement, hyoid-mental distance and oropharyngeal status (e.g. mouth opening and Mallampati classification).[12]

Statement 15: Training in sedation should be structured. There should be assessment of competencies prior to the independent administration of sedation.

Quality of evidence: Low

Strength of recommendation: Strong

Agreement: 100%

Training in sedation pharmacology and recognition of the different levels of sedation can be taught in theory, often taking the form of instructional videos with quizzes at the end of these videos in the local setting. These are required for proceduralists starting training in GI endoscopy and are valid for a defined duration, often 2 to 3 years, before a refresher course is required. Sedation training curriculums have been published by professional societies in the US (American Gastroenterological Association [AGA], American College of Gastroenterology [ACG], American Society for Gastrointestinal Endoscopy [ASGE], American Association for the Study of Liver Diseases [AASLD] and Society of Gastroenterology Nurses and Associates. [SGNA])[130] and in Europe (European Society of Gastrointestinal Endoscopy [ESGE] and European Society of Gastroenterology and Endoscopy Nurses and Associates [ESGENA]).[131] In Singapore, trainees are under direct supervision while undergoing training in GI endoscopy. There is also hands-on supervision in the actual administration of sedation. This is consistent with the training recommendations from the US[129] and Europe.[131] The ability to manage adverse events from sedation is also an important part of training. The ESGE/ESGENA curriculum recommends that all endoscopists and sedationists be trained in basic cardiac life support. In addition, those practising in facilities where an advanced cardiac life support (ACLS) provider is not immediately available should also be trained in ACLS.[110,131] The AGA/ACG/ASGE/AASLD/SGNA curriculum recommends that all endoscopists and sedationists be trained in ACLS or its equivalent.[129] The assessment of competency in the safe use of sedation in GI endoscopy may vary in different countries and healthcare systems.[131-133] In the Singapore context, the assessment of trainee competency is under the purview of bodies such as the Residency Advisory Committee (RAC) that oversees specialist training at the national level, and the Clinical Competencies Committees (CCC) of the respective institutions offering training in GI endoscopy.

The workgroup agrees with the recommendation from ESGE/ESGENA that ACLS training of the endoscopist or sedationist is required only in the context of facilities without a code blue team. European endoscopic sedation data after the introduction of these European training guidelines have demonstrated the safety and effectiveness.[73] Despite more widespread adoption of sedation during endoscopy including the use of propofol by non-anaesthesiologists, sedation-related complications have remained low.[134] American data from the same period showed increased adoption of anaesthesiologist-administered sedation (in up to 53% of commercially insured patients) with increased cost and utilisation of limited anaesthesiology resources even for ASA 1 and 2 patients.[1,135]

Statement 16: Non-anaesthesiologists using propofol for sedation should have additional training with respect to propofol. They should have training for resuscitation with emphasis on airway management.

Quality of evidence: Low

Strength of recommendation: Strong

Agreement: 88.9%

Data demonstrated the safety and efficacy of non-anaesthesiologist-administered propofol sedation (NAAP). NAAP requires specialised training, patient selection, and personnel dedicated to continuous physiologic monitoring.[12,132] The current sedation training for endoscopy trainees in Singapore focuses only on the safe and effective use of benzodiazepines and opiates. Hence, there should be additional structured training on the safe use of propofol. Unlike benzodiazepines and opiates, there are no reversal agents for propofol. Hence the ability to manage adverse events such as airway compromise from propofol is even more crucial. Training curricula have been published in the US by AGA/ACG/ASGE/AASLD/SGNA[130] and in Europe by ESGE/ESGENA.[110,131] The Korean NAAP training guideline developed by anaesthesiologists is similar to the ESGE guideline.[136] Propofol can be safely used by non-anaesthesiologists for endoscopic sedation after rigorous training.[137] As training in the use of propofol is currently not incorporated during training for GI endoscopy, a dedicated formal structured course on the use of propofol would be needed for endoscopists intending to provide NAAP if they do not have prior experience in its usage. ACLS training will also be required if propofol sedation is administered in a centre without a code blue team. The training course should involve all relevant stakeholders, and could potentially be organised under the auspices of AMS, or specific institutions or professional bodies. In current clinical practice, propofol sedation is already being administered safely by non-anaesthesiologists in the private practice setting. These doctors would have either undergone formal or informal training on the use of propofol in the past and should be allowed to continue this practice based on past track records. Individual institutions may consider the need for specific credentialling. For non-anaesthesiologists who now intend to begin providing propofol sedation, formal training would be recommended.

CONCLUSION

This is the first AMS guideline for sedation during GI endoscopy by non-anaesthesiologists in the hospital setting, summarising the available evidence according to GRADE, and making recommendations by the modified Delphi process. The guideline addresses pre-, peri- and post-procedural issues related to the administration of sedation during GI endoscopy, provides evidence-based appraisal of the efficacy and safety of benzodiazepines, opiates and propofol. The guideline also addresses the roles of anaesthesiologists and non-anaesthesiologists in the administration of sedation. In particular, it addresses the use of propofol by non-anaesthesiologists. It is hoped that this guideline would enhance the safety and quality of sedation during GI endoscopy by non-anaesthesiologists. At the same time, it is also important that individual hospitals track and audit adverse outcomes arising from the provision of sedation during GI endoscopy. This guideline will be revised as necessary to cover progress and changes in technology, and evidence from clinical practice.

Disclosure

The guideline was commissioned by the Academy of Medicine, Singapore.

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REVIEW ARTICLE

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Trauma-induced coagulopathy: Mechanisms and clinical management

Vui Kian Ho [1]*FANZCA*, Jolin Wong [1]*FANZCA*, Angelly Martinez [2]*FCICM*, James Winearls [2]*FCICM*

ABSTRACT

Introduction: Trauma-induced coagulopathy (TIC) is a form of coagulopathy unique to trauma patients and is associated with increased mortality. The complexity and incomplete understanding of TIC have resulted in controversies regarding optimum management. This review aims to summarise the pathophysiology of TIC and appraise established and emerging advances in the management of TIC.

Methods: This narrative review is based on a literature search (MEDLINE database) completed in October 2020. Search terms used were "trauma induced coagulopathy", "coagulopathy of trauma", "trauma induced coagulopathy pathophysiology", "massive transfusion trauma induced coagulopathy", "viscoelastic assay trauma induced coagulopathy", "goal directed trauma induced coagulopathy and "fibrinogen trauma induced coagulopathy'.

Results: TIC is not a uniform phenotype but a spectrum ranging from thrombotic to bleeding phenotypes. Evidence for the management of TIC with tranexamic acid, massive transfusion protocols, viscoelastic haemostatic assays (VHAs), and coagulation factor and fibrinogen concentrates were evaluated. Although most trauma centres utilise fixed-ratio massive transfusion protocols, the "ideal" transfusion ratio of blood to blood products is still debated. While more centres are using VHAs to guide blood product replacement, there is no agreed VHA-based transfusion strategy. The use of VHA to quantify the functional contributions of individual components of coagulation may permit targeted treatment of TIC but remains controversial.

Conclusion: A greater understanding of TIC, advances in point-of-care coagulation testing, and availability of coagulation factors and fibrinogen concentrates allows clinicians to employ a more goal-directed approach. Still, hospitals need to tailor their approaches according to available resources, provide training and establish local guidelines.

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Keywords: Blood coagulation disorders, fibrinolysis, massive haemorrhage, transfusion, trauma

INTRODUCTION

Globally, trauma accounts for the highest number of mortalities in adolescents and young adults up to 49 years old.[1] Of these deaths, a large percentage is attributable to exsanguination.[2] Trauma-induced coagulopathy (TIC) occurs in 25–35% of hospitalised severe trauma patients and is associated with increased incidence of bleeding, blood transfusion, multiorgan failure and death.[3]

The main feature seen in TIC is reduction in clot strength, or absent clot formation. This arises from endothelial dysfunction, platelet dysfunction, hypofibrinogenemia or dysfibrinogenemia and hyperfibrinolysis, and is exacerbated by acidosis, hypothermia, haemodilution and factor consumption related to massive blood loss and large volumes of fluid resuscitation (Fig. 1).[4,5]

However, TIC is more appropriately renamed "coagulopathic response to trauma" because the coagulopathy is not a uniform phenotype, with a thrombotic phenotype at one end and a bleeding phenotype at the other, with a series of mixed thrombotic-bleeding phenotype along the spectrum.[3] Both thrombotic and bleeding phenotypes are associated with increased mortality.

[1] Surgical Intensive Care, Division of Anaesthesiology, Singapore General Hospital, Singapore
[2] Intensive Care Medicine, Gold Coast University Hospital, Queensland, Australia
Correspondence: Dr Vui Kian Ho, Surgical Intensive Care, Division of Anaesthesiology, Singapore General Hospital, Outram Road, Singapore 169608.
Email: ho.vui.kian@singhealth.com.sg

CLINICAL IMPACT

What is New

- This review summarises the latest understanding of the complex pathophysiology of trauma-induced coagulopathy (TIC) and appraises established and emerging advances in the management of TIC.

Clinical Implications

- TIC is a spectrum of phenotypes ranging from thrombotic to bleeding phenotypes. There is no single protocol that universally addresses TIC.
- Viscoelastic haemostatic assays can quantify the functional contributions of individual components of coagulation and permit targeted treatment of TIC but remains controversial.
- Better understanding of TIC, advances in point-of-care coagulation testing, and availability of coagulation factors and fibrinogen concentrates allow clinicians to employ a more goal-directed approach.

This narrative review is based on a literature search (MEDLINE database) completed in October 2020. Search terms used were "trauma induced coagulopathy", "coagulopathy of trauma", "trauma induced coagulopathy pathophysiology", "massive transfusion trauma induced coagulopathy", "viscoelastic assay trauma induced coagulopathy", "goal directed trauma induced coagulopathy" and "fibrinogen trauma induced coagulopathy". We aim to summarise the recent science on the pathophysiology of TIC and appraise both established and emerging advances in management, like goal- and diagnostic-directed therapy, as well as factor and fibrinogen concentrates.

Pathophysiology of TIC

Several mechanisms have been proposed to explain the development of TIC. The hyperfibrinolysis and coagulopathy seen in TIC are chiefly due to the effects on the endothelium related to shock, hypoperfusion and direct tissue injury.[6] The concept of tissue injury as the driving force behind TIC is seen in that coagulopathy is present even before fluid resuscitation or massive transfusion, and correlates with severity of trauma.[7,8]

Hyperfibrinolysis

Endothelial thrombomodulin expression is upregulated in response to tissue hypoperfusion, and together with thrombin generated by tissue trauma, forms thrombomodulin–thrombin complex that accelerates protein C activation. Activated protein C causes coagulopathy by inactivating factors Va and VIIIa, and produces fibrinolysis by inactivating plasminogen activator inhibitor 1 (PAI-1).[6,9] A study by Chapman et al. demonstrated that endothelial tissue plasminogen activator (tPA) overexpression is necessary for hyperfibrinolysis to occur because tPA forms a covalent complex with PAI-1.[10] A functional assay for PAI-1 reserve was devised using thromboelastography (TEG) with exogenous tPA challenge. Chapman et al. concluded that because severe hypoperfusion activates endothelial cells to release tPA from Weibel–Palade bodies into the systemic circulation, the excess tPA sequesters PAI-1 into the inactive complex, thereby decreasing PAI-1 activity.

Fibrinolysis shutdown

On the opposite end of the fibrinolysis phenotype are patients who demonstrate fibrinolysis shutdown, which is associated with impaired tPA release following trauma.[3] Fibrinolysis shutdown is a common phenotype and is associated with higher mortality than in patients with physiologic fibrinolysis.

This was demonstrated in a prospective study by Moore et al., who categorised patients with severe trauma based on fibrinolysis characteristics: fibrinolysis shutdown (clot lysis at 30 minutes after maximum clot strength [LY30]<0.8%), physiologic lysis (LY30 0.8–3%) and hyperfibrinolysis (LY30>3%).[11] There were no significant differences in baseline characteristics, including injury patterns or severity scores. Of the 32 patients with physiologic lysis, 3% died. Mortality rate increased to 17% for patients with fibrinolysis shutdown (n=33) and was 44% in patients with hyperfibrinolysis (n=115). Notably, deaths in patients with hyperfibrinolysis were mainly from massive haemorrhage, whereas deaths in patients with fibrinolysis shutdown occurred later from multiorgan failure, postulated to be from fibrin deposits in the microcirculation. Gall et al. similarly characterised 3 fibrinolysis phenotypes in 914 patients based on maximum lysis (ML) rates from rotational thromboelastometry: hyperfibrinolysis (ML>15%), physiologic fibrinolysis (ML 5–15%) and fibrinolysis shutdown (ML<5%).[12] The mortality pattern was similar to that described by Moore et al.

Endothelial factors

The endothelial glycocalyx, and its effects on the neurohormonal axis, is involved in the development of TIC. The rise in systemic catecholamine levels following trauma and haemorrhagic shock exacerbates

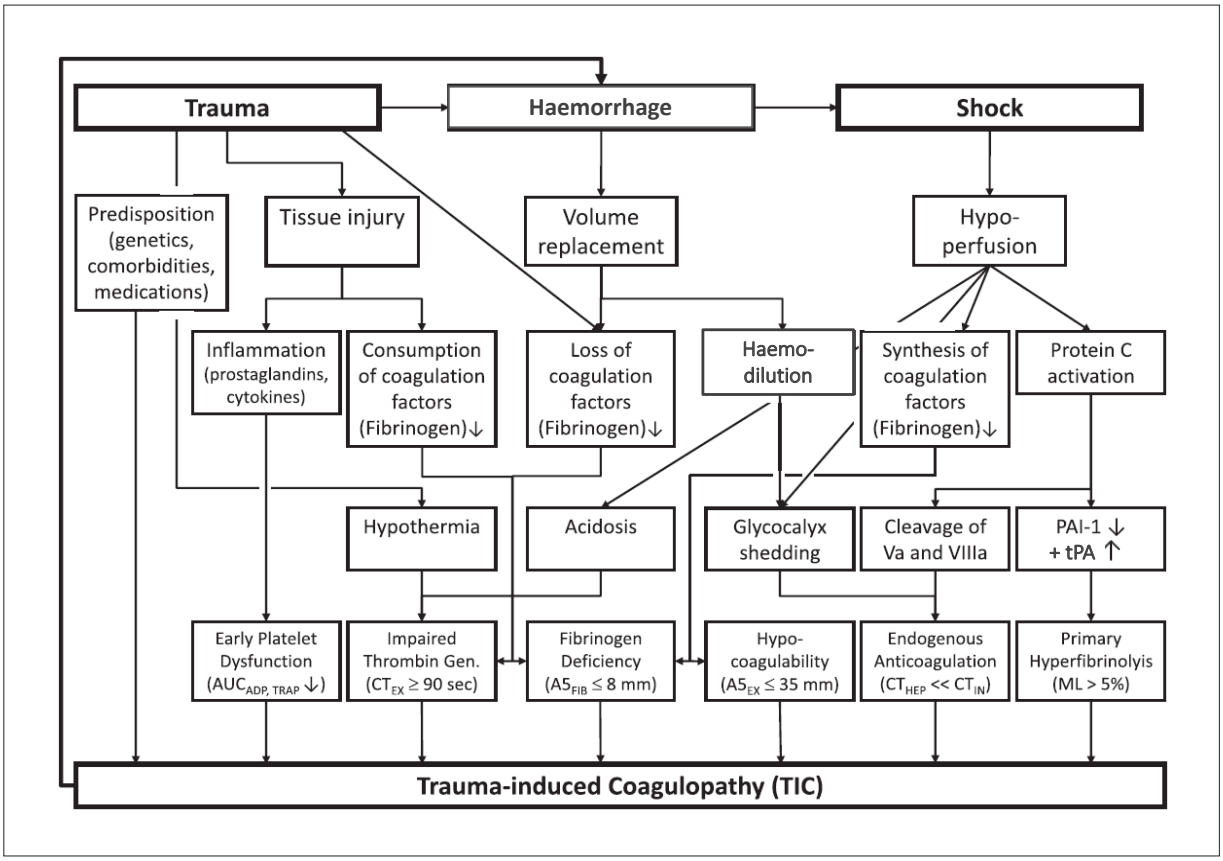

Fig. 1. Pathophysiology of trauma-induced coagulopathy and its detection by thromboelastometry. (Modified from Winearls J, et al. Targeted coagulation management in severe trauma: the controversies and the evidence. Anesth Analg 2016;123:910-24, with permission from Wolters Kluwer Health, Inc.)

A5EX: amplitude 5 minutes after coagulation time in EXTEM; A5FIB: amplitude 5 minutes after coagulation time in FIBTEM; ADP: adenosine diphosphate; AUC: area under the curve in impedance aggregometry (in thromboelastometry platelet); CT: coagulation time; CTEX: coagulation time in EXTEM; CTHEP: coagulation time in HEPTEM; CTIN: coagulation time in INTEM; ML: maximum lysis (within 1 hour run time); PAI-1: plasminogen activator inhibitor-1; Thrombin Gen.: thrombin generation; TRAP: thrombin receptor–activating peptide

endothelial glycocalyx degradation, which can be associated with auto-heparinisation and increased mortality.[13-15] Animal studies done demonstrated glycocalyx restoration following resuscitation with plasma, suggesting a different mechanism than merely replacement of coagulation factors.[14] This effect of endothelial repair was similar in a 4-factor prothrombin complex concentrate, but was not observed following resuscitation with crystalloids or albumin.[16]

Platelet and fibrinogen dysfunction

The cell-based model of haemostasis recognises the role of platelets and fibrinogen in the stages of coagulation.[17] In trauma, however, there remains limited understanding of the pathogenesis of platelet and fibrinogen dysfunction. Platelet levels in early trauma are usually not inordinately depressed to the point that coagulation is compromised. Despite this, evidence has shown that platelet transfusion improves haemostasis in trauma. The Prospective, Observational, Multicenter, Major Trauma Transfusion (PROMMTT) and the Pragmatic, Randomized Optimal Platelet and Plasma Ratios (PROPPR) studies illustrate that rates of exsanguination may be reduced if platelet transfusions are initiated in the early stages (within 24 hours) following severe trauma.[18,19] Furthermore, the latter suggested that a 1:1:1 ratio of plasma, platelets and red blood cells was superior to a 1:1:2 ratio in achieving haemostasis, with no increase in complications.[19] This raises a possibility that platelet dysfunction, rather than a reduced platelet count, contributes to TIC. Several studies have investigated platelet aggregation after trauma and found poorer outcomes in instances of platelet dysfunction.[20,21] Platelet dysfunction may also be associated with increased sensitivity to exogenous fibrinolytic stimuli and thereby enhanced hyperfibrinolysis.[22] Meizoso et al. showed that platelet transfusion in the first week was associated with a dose-

dependent risk of persistent fibrinolysis shutdown.[23] Platelets contain large quantities of PAI-1 and α2 antiplasmin and Vulliamy et al.'s study suggests that platelet transfusion decreases fibrinolysis due to high PAI-1 levels.[24]

Fibrinogen levels may be decreased as early as the point of admission and low fibrinogen levels are associated with poorer outcomes including higher mortality.[25-27]

While the exact pathophysiology is still poorly understood, the literature is clear: TIC is associated with increased mortality.[28,29] As more evidence emerges, the management of TIC will also likely change with our understanding.[30] For example, it may be possible to tailor treatment based on the identification of a patient's phenotype through viscoelastic haemostatic assays (VHAs) or other biomarkers.[3]

Management of TIC

The management of TIC has evolved with increased knowledge and advances in diagnostics and therapeutics, and involves addressing the many factors in the pathophysiology of TIC.[31] This section will explore the management options, starting with more established and cruder methods and progressing to more goal-directed and diagnostic-guided approaches.

Tranexamic acid

The CRASH-2 trial was a landmark study, which demonstrated that the use of tranexamic acid in adult trauma was associated with a reduction in all-cause mortality compared with placebo.[32] Subsequent exploratory analysis showed that the delayed use of tranexamic acid beyond 3 hours was associated with increased risk of death due to bleeding, thus supporting early administration.[33] However, tranexamic acid has been associated with increased rates of venous thromboembolism.[34] Since the publication of the study, the use of tranexamic acid has been debated extensively and the evidence remains controversial.[35] Nevertheless, its benefit has been corroborated in other studies,[36] and international guidelines have recommended its use within the first 3 hours following trauma.[31]

Massive transfusion protocols

Massive transfusion protocols represent a balanced resuscitative strategy for the rapid delivery of large volumes of blood products in a predefined ratio in the treatment of haemorrhagic shock.[37] There is no single correct strategy, and as such individual institutions differ widely in the trigger threshold for initiation of the massive transfusion protocols as well as the predefined ratios of blood products.[38] Despite these institutional and geographical variations, it remains evident that massive transfusion protocols reduce mortality.[39]

The PROMMTT study demonstrated improved 24-hour survival with transfusions of higher ratios of plasma and platelets at an early stage in resuscitation.[18] The 2015 multicentre PROPPR trial found no difference in the 24-hour or 30-day mortality between a 1:1:1 ratio versus a 1:1:2 ratio of plasma to platelets to RBCs transfused.[19] However, the group that received a 1:1:1 ratio was more likely to achieve haemostasis and less likely to die from exsanguination.

Although conventionally, a fixed ratio of blood product transfusion has been recommended, there has been increasing use of coagulation factor concentrates as an alternative to fresh frozen plasma (FFP) in the correction of trauma-induced coagulopathy. A significant concern with the use of large volumes of blood products is the potential for transfusion-associated circulatory overload and transfusion-related acute lung injury.[40]

Goal-directed transfusion

Our limited understanding of the mechanisms of TIC suggests that there is no one-size-fits-all approach for massive transfusion protocols in predetermined, fixed ratios in all patients. The heterogenous nature of trauma necessitates treatment that is targeted to the individual patient's needs. In contrast to a universal transfusion protocol, a targeted approach to each patient theoretically guides individualised therapy. Goal-directed therapy is a Grade 1B recommendation in the recent European guidelines and can be achieved using standard laboratory tests (SLT) or point-of-care assays.[31] A single-centre randomised controlled trial compared severe trauma patients who were administered a transfusion protocol guided by laboratory results with those administered a fixed-ratio transfusion protocol.[41] This study showed reduced plasma wastage with a goal-directed protocol and reduced 28-day mortality in the intention-to-treat analysis. Two other studies showed that a change in protocol incorporating goal-directed transfusion was associated with a reduction in the use of blood products, a trend to mortality reduction and reduced healthcare costs.[42,43] However, these were single-centre studies and were underpowered with small sample sizes.

The Strategy of Transfusion in Trauma (STATA) trial compared a fixed ratio protocol (1:1:1) to a TEG-guided administration of coagulation factor concentrates and fibrinogen in patients with major trauma. While the study has not been published, the interim analysis showed no difference in mortality.[44]

Viscoelastic haemostatic assays

Conventional coagulation studies (prothrombin time and activated partial thromboplastin time) test isolated portions of the coagulation cascade in a laboratory, and may not be indicative of true clotting in vivo. There is also no functional measure of clot strength or fibrinolysis in a conventional coagulation test. Furthermore, the need to perform such tests in a centralised laboratory implies an inevitable delay in obtaining results necessary to make decisions on further blood product transfusion. VHAs, on the other hand, examine clotting dynamics in whole blood and reveal the interactions between the cellular and plasma components of blood up to fibrinolysis. The use of VHAs allows the examination of different stages in the coagulation cascade, with specific information on the initiation of haemostasis, clotting kinetics, clot strength and clot stability (or lysis) [45] Finally, VHAs are available as point of care tests with almost real-time feedback to the managing clinician.

There are two main systems available for VHAs: the thromboelastogram (TEG Hemostasis Analyzer System) (Haemonetics, Boston, US) and rotational thromboelastometry (ROTEM) (TEM Innovations GmbH, Munich, Germany). A systematic review suggested that VHAs diagnose early trauma coagulopathy and may predict transfusion and mortality.[46]

TEG has been found to be a better predictor of the need for transfusion of individual blood product components compared with SLTs (prothrombin time, activated partial thromboplastin time, platelets and fibrinogen).[47] A prospective randomised controlled trial comparing goal-directed TEG-based transfusion with SLT-based transfusion showed that mortality in the VHA group was significantly reduced (19.6% vs 36.4%).[48] Both groups used a similar number of RBC units, but the SLT group used more plasma and platelet units in the early phase of resuscitation. However, this was a single-centre study and patients were randomised by weekly alternation of treatment arms. Moreover, 8 of 55 patients randomised to SLT crossed over to the VHA protocol at the request of treating physicians, which could introduce bias from non-adherence.

The Implementing Treatment Algorithms for the Correction of Trauma-Induced Coagulopathy (iTACTIC) multicentre randomised controlled trial compared the use of VHA-guided with SLT-guided transfusion in 396 adult trauma patients with haemorrhagic shock that activated the local massive haemorrhage protocol.[49] Patients were block randomised per centre and followed up until discharge or day 28. There was no difference in the primary endpoint, which was the proportion of subjects alive and free of massive transfusion (less than 10 units of RBCs) at 24 hours. There were also no differences in secondary outcomes such as the rate of organ failure, total hospital and intensive care length-of-stay, healthcare resources needed, and mortality.

Despite a lack of high-quality evidence, the use of VHAs has been advocated during massive transfusion in various trauma centres and recommended in trauma management guidelines.[31,50,52] An example of a hospital VHA-guided transfusion algorithm is shown in Fig. 2.

A hybrid approach has also been proposed that involves the initial use of ratio-driven massive blood transfusion, followed by goal-directed therapy at a later stage.[53-55] This hybrid approach is supported by the European guidelines, which recommend that the initial management of bleeding and coagulopathy consist of antifibrinolytic agents, coagulation monitoring and support, and notably, initial coagulation resuscitation

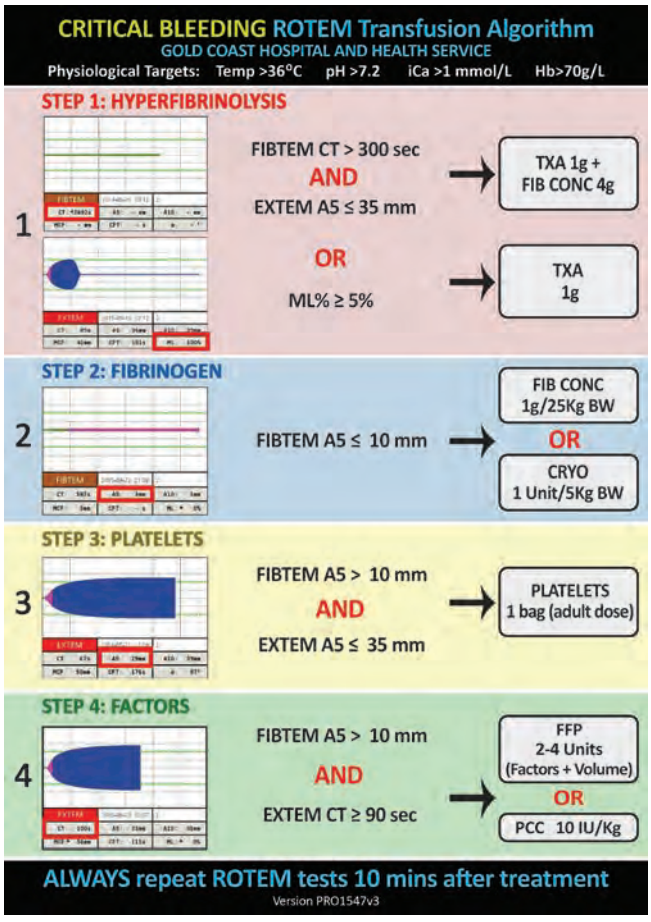

Fig. 2. Gold Coast University Hospital ROTEM trauma algorithm. (Reproduced with permission from Gold Coast University Hospital.)

A5: amplitude 5 minutes after coagulation time; A10: amplitude 10 minutes after coagulation time; BW: body weight; CFT: clot formation time; CRYO: cryoprecipitate; CT: coagulation time; FFP: fresh frozen plasma; FIB CONC: fibrinogen concentrate; MCF: maximum clot firmness; ML: maximum lysis; PCC: prothrombin complex concentrate; ROTEM: thromboelastometry; TXA: tranexamic acid

with FFP in a FFP:RBC ratio of at least 1:2, or fibrinogen concentrate and RBC. This is followed by further goal-directed coagulation management, in which FFP, coagulation factor concentrates, fibrinogen supplementation, platelets and calcium are replaced with goal-directed therapy guided by SLT or VHA.[31]

Coagulation factor concentrates

The use of coagulation factor concentrates as first-line therapy enables faster correction and reduces the volume of blood products transfused with a potential for fewer side effects from plasma administration.[56] A nationwide retrospective study examined outcomes of severely injured trauma patients receiving both 4-factor prothrombin complex concentrate and FFP compared with FFP alone, utilising the American College of Surgeons Trauma Quality Improvement Program database.[57] Patients were matched into 2 groups of 234 each. Using propensity-matched analysis, 4-factor prothrombin complex concentrate together with FFP was associated with decreased packed RBC and FFP requirements, lower mortality (17.5% vs 27.7%, P=0.01) and decreased rates of acute respiratory distress syndrome and acute kidney injury. Further randomised controlled trials are needed to better evaluate the role of prothrombin complex concentrate in major trauma.

Fibrinogen concentrate

The early use of fibrinogen concentrate was explored in the fibrinogen in the initial resuscitation of severe trauma (FiiRST) trial.[58] This randomised, placebo-controlled feasibility study of 50 hypotensive trauma patients showed increased plasma fibrinogen levels in the fibrinogen concentrate group, with 96% of subjects receiving the intervention within 1 hour. In the blinded, randomised, placebo-controlled trial of early fibrinogen concentrate therapy for major haemorrhage in trauma (E-FIT-1)[59] involving adult trauma patients at 5 major trauma centres who required activation of major haemorrhage protocol, subjects were to receive either 6g of fibrinogen or placebo within 45 minutes of admission. However, only less than 70% of subjects received the study intervention in the stipulated time, suggesting that this protocol is not feasible in practice.

The Reversal of Trauma Induced Coagulopathy (RETIC) trial was a single-centre, open-label, randomised trial in Austria that compared the use of FFP with fibrinogen concentrate.[60] The study included adult patients with major trauma who had coagulopathy identified using rotational thromboelastometry. It was terminated early because of the harmful effect of massive transfusion in the plasma arm. The primary endpoint of multiorgan failure was found to be increased in the plasma arm, although this was not statistically significant owing to the early termination of the study. The targeted use of fibrinogen concentrates was associated with earlier correction of coagulopathy, reduced transfusion of blood products and decreased rate of massive transfusion.

Platelet function analysers

The use of antiplatelet medication is common internationally and poses a bleeding risk in the setting of trauma. Point-of-care platelet function tests identify the presence of platelet dysfunction[61] and have the potential to guide blood product transfusion. The 2019 European guidelines have suggested the use of point-of-care platelet function devices as an adjunct to SLT or VHA in patients with suspected platelet dysfunction.[31] A single-centre study compared the use of TEG platelet mapping with impedance aggregometry in 52 patients in a level 1 trauma population.[62] Results revealed weak correlation in the adenosine diphosphate channel and a moderate correlation in the arachidonic acid channel. TEG platelet mapping predicted blood product transfusion and correlated with increased base deficit, while impedance aggregometry was more predictive of mortality. The utility and validity of platelet function analysers are still evolving.

Upcoming studies of interest

We look forward to the currently recruiting Pre-hospital Anti-fibrinolytics for Traumatic Coagulopathy and Haemorrhage (PATCH) Study, a multicentre, randomised, double-blinded, placebo-controlled trial, which is investigating whether extending tranexamic acid administration to the prehospital setting for severely injured patients at risk of TIC will improve mortality and functional recovery at 6 months.[63] This could push the established practice of early tranexamic acid administration even earlier.

While the early use of fibrinogen concentrate has theoretical value, the E-FIT 1 trial showed issues with protocol implementation.[59] We therefore await the publication of the Fibrinogen Early in Severe Trauma (FEISTY) study.[64] This is a multicentre, randomised controlled trial comparing the use of rotational thromboelastometry-guided fibrinogen concentrate to cryoprecipitate for fibrinogen replacement in adults with traumatic haemorrhage.

Finally, early fibrinogen supplementation with high-dose cryoprecipitate, within 3 hours of injury, in adult

patients with severe trauma and major haemorrhage is being studied in the ongoing CRYOSTAT-2 trial.[65] It is a multicentre, randomised controlled trial aiming to recruit over 1,500 patients and will compare the intervention with standard therapy on 28-day all-cause mortality. This trial was done following the successful CRYOSTAT-1 feasibility study,[66] in which 86% of patients received cryoprecipitate within 90 minutes of admission.

With increasing recognition that the higher proportion of plasma found in most massive transfusion protocols may be harmful to patients, these upcoming studies that explore the use and timing of fibrinogen concentrate and cryoprecipitate will inform us if they provide better outcomes compared with the plasma-heavy approach to transfusion.

CONCLUSION

A greater understanding of TIC, coupled with advances in point-of-care coagulation testing and availability of coagulation factors and fibrinogen concentrates, allows the clinician to employ a more goal-directed approach to massive transfusion, as opposed to traditional fixed-ratio approaches. However, to achieve best outcomes, hospitals need to tailor their approaches according to available resources, provide adequate training and establish local guidelines or algorithms.[31] Ultimately, no matter the approach, the patient will be best cared for by a highly skilled team of trauma surgeons, anaesthetists and critical care physicians trained in damage control resuscitation and surgery.

Acknowledgement

This article is dedicated to the memory of a wonderful colleague and friend, Dr Jeremy Ng Chung Fai, who passed away in 2020.

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LETTER TO THE EDITOR

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Labour epidural practice in a tertiary training centre

Dear Editor,

Labour analgesia provided through the central neuraxial approach is offered for parturients who are in their active stage of labour, usually after 2–4cm of cervical dilatation. Lumbar epidural, the gold standard for labour analgesia, is recently recommended over other alternative methods of analgesia such as pressurised gaseous nitrous oxide, to minimise aerosol-related risks to healthcare teams.[1] The labour epidural procedure requires advanced technical regional anaesthetic skills. It is uniquely associated with immense pressure to achieve time-sensitive procedural success, as patients vocalise the unbearability of pain while the next of kin are present in the delivery suite room. The difficulties encountered are the unstable or frequently shifting patient positioning that dynamically alters the access to the epidural and subarachnoid space; anatomical changes in pregnancy; exaggerated lumbar lordosis; and distended epidural blood vessels during frequent active contractions.[2] Maternal obesity further compounds this, resulting in adverse outcomes.[3]

Opportunities for learning non-obstetric epidural analgesia have significantly reduced due to the introduction of surgeon-led infiltration-analgesic practices, and truncal plane blocks such as the erector spinae plane (ESP).[4] The introduction of protocol-based enhanced recovery after surgery (ERAS) has limited the use of central neuraxial blockade to facilitate early ambulation. This has resulted in obstetric labour epidurals being the first epidural technique that the trainees tend to perform on patients.

To address these gaps, trainees receive structured simulation-based knowledge, skills and cognitive training before they are allowed to perform epidurals on parturients.[5] These include proficiency in technical skills achieved on epidural part-task trainer mannequins, followed by apprenticeship model of clinical observation and guided actual hands-on experiences. Crisis management and interprofessional team-based simulations are introduced subsequently to master the attributes of situational awareness and enhanced closed-loop communications.

The existing system of supervision of trainees emulates the entrustable professional activity-based models,[6,7] where they are stratified based on their individual ability to perform the epidural procedure with technical accuracy, identify clinical variations (obesity and scoliosis), recognise patterns of complications (accidental dural puncture and intravascular epidural misplacement) and to promptly escalate when clinical acute deteriorations (maternal hypotension and local anaesthetic toxicity) occur. There is limited data clarifying whether epidural procedures performed by trainees were as safe as those done by specialists. There were inconsistent practices on how an epidural procedure is offered for trainees to attempt. These included mere electronic medical review of body weight and body mass index (BMI), and not by a structured assessment of anticipated difficulty by clinical evaluation. Cohort-based data on the anatomical variations and reported difficulties between various ethnicities and nationalities were limited.

We report a retrospective cohort study (December 2017 to May 2018), with data accessed through the electronic health records (computerised patient support system [CPSS] 2, Integrated Health Information Systems, Singapore) at National University Hospital, Singapore (full review: NHG-DSRB 2018/00453). The study included the review of scanned records of labour epidural procedures, pain audits and incidents reported in the immediate peripartum period until discharge. The data was analysed by SPSS Statistics software version 24.0 (IBM Corp, Armonk, US).

A total of 912 patients who received central neuraxial blockade for labour analgesia were screened. After excluding those with incomplete documentation, data from 727 patients were analysed. Of the patients analysed, 639 (87.9%) received combined spinal epidural analgesia, 87 (12.0%) received plain epidural analgesia and in 1 (0.1%), the technique was unreported.

Majority of patients (41.4%) belonged to the overweight category (BMI mean 27.96, standard deviation 5.17) and epidural depth was found to moderately correlate (r=0.53) with BMI (3.3cm in BMI<18 to 6.5cm in BMI>40). The cohort included patients stratified based on their ethnicities and further by nationalities within the same ethnicities. The population distribution of the ethnicities included patients of Chinese origin (46%), Malay (20%), Indian (17%), Caucasian (3%) and other ethnicities (14%). The proportion of nationalities varied among the different ethnicities (e.g. Chinese: 30% expatriate, 70% local; Indian: 63% expatriate, 37% local).

Majority of epidurals (90%) in Caucasians were achieved in the first attempt compared to 75% for

Table 1. Distribution of ethnicities, level of epidural difficulty and complications

Parameters	Details	Chinese	Malay	Indian	Others	Caucasian	All
	No. (%)	334 (45.9)	146 (20.1)	121 (16.6)	105 (14.4)	21 (2.9)	727 (100)
BMI[a]	Average	26.2	30.7	29.5	28.2	26.3	28.0
Number of attempts	1	252 (75.4)	102 (69.9)	79 (65.3)	71 (67.6)	19 (90.5)	523 (71.9)
	2	49 (14.7)	23 (15.8)	24 (19.8)	16 (15.2)	1 (4.8)	113 (15.5)
	>2	28 (8.4)	18 (12.3)	18 (14.9)	15 (14.3)	0	79 (10.9)
	NE	5 (1.5)	3 (2.1)	0	3 (2.9)	1 (4.8)	12 (1.7)
Complications[b]	Paraesthesia	13 (3.9)	11 (7.5)	11 (9.1)	6 (5.7)	0	41 (5.6)
	Venous tap	10 (3.0)	3 (2.1)	4 (3.3)	3 (2.9)	0	20 (2.8)
	Dry tap	6 (1.8)	3 (2.1)	0	1 (1.0)	0	10 (1.4)
	Others	6 (1.8)	0	2 (1.7)	1 (1.0)	1 (4.8)	10 (1.4)
	Hypotension	1 (0.3)	2 (1.4)	2 (1.7)	0	1 (4.8)	6 (0.8)
	Overall	34 (10.2)	17 (11.6)	17 (14.0)	11 (10.5)	2 (9.5)	81 (11.1)
Lumbar spine level	L2-L3	17 (5.1)	4 (2.7)	5 (4.1)	4 (3.8)	0	30 (4.1)
	L3-L4	233 (69.8)	121 (82.9)	96 (79.3)	77 (73.3)	19 (90.5)	546 (75.1)
	L4-L5	87 (26.0)	23 (15.8)	23 (19.0)	22 (21.0)	2 (9.5)	157 (21.6)
	L5-S1	2 (0.6)	0	1 (0.8)	0	0	3 (0.4)
Epidural depth	Average, cm	4.6	5.0	4.9	4.6	4.7	4.7
Breakthrough pain[c]	Incidence	48 (14.4)	25 (17.1)	16 (13.2)	11 (10.5)	4 (19.0)	104 (14.3)
Epidural regime	Infusion	197 (59.0)	110 (75.3)	75 (62.0)	68 (64.8)	12 (57.1)	462 (63.5)
	PCEA+PIB	112 (33.5)	28 (19.2)	38 (31.4)	30 (28.6)	7 (33.3)	215 (29.6)
	NE	25 (7.5)	8 (5.5)	8 (6.6)	7 (6.7)	2 (9.5)	50 (6.9)
>2 attempts[d]	BMI <18	0	0	0	0	0	0
	BMI >18–25	6 (4.3)	2 (7.1)	3 (16.7)	3 (12.5)	0	14 (6.5)
	BMI >25–30	17 (11.9)	1 (2.8)	6 (10.5)	4 (7.5)	0	28 (9.3)
	BMI >30–35	4 (8.9)	8 (15.7)	6 (19.4)	7 (35.0)	0	25 (16.8)
	BMI >35–40	1 (20.0)	4 (21.1)	3 (23.1)	0	0	8 (19.5)
	BMI >40	0	3 (27.3)	0	1 (25.0)	0	4 (22.2)
Specialist epidurals (subgroup analysis)	Complications	23 (9.7)	8 (13.3)	12 (13.2)	9 (11.3)	2 (11.1)	54 (11.1)
	No complications	214 (90.3)	52 (86.7)	79 (86.8)	71 (88.8)	16 (88.9)	432 (88.9)
	More than 2 attempts	13 (5.4)	7 (11.7)	10 (11.0)	9 (11.3)	0	39 (8.0)

BMI: body mass index; NE: not entered or data unavailable; PCEA: patient-controlled epidural analgesia; PIB: programmed intermittent bolus
[a] BMI was calculated objectively by documented weight and height in electronic health records at the time of booking
[b] Complications exclude breakthrough pain
[c] Epidural infusions had higher breakthrough pain (14.5%) compared to PCEA+PIB (13.5%)
[d] Attempt is defined as number of reinsertions with new skin puncture and excludes the re-directions of needle during same insertion. Epidural depth can vary between the lumbar levels of same patient; an average is presented above.

Chinese, 70% for Malay and 65% for Indian ethnicities. The rate of complications (residual neuropraxia, accidental dural puncture, etc.) was found to be highest in Malay ethnicity (25.7%) followed by Indian (24.6%), Caucasian (23.8%), Chinese (20.9%) and Others (19%) (Table 1). Logistic regression analysis showed 3 times higher odds of incidence of complications (P=0) if more than 2 attempts were needed for epidural placement.

Specialists with more than 5 years of experience performed 67% of epidurals. There were no significant differences in the overall rate of complications among the epidurals performed by specialists (11%), trainees (12%) and those performed by trainees that eventually required specialist support (10%). This data reaffirmed the safety of existing structured training and supervision when labour epidurals are performed by trainees. Experienced midwives present in the procedure rooms are trained to summon for specialist presence when trainees struggle with technical complexities, providing parturients with an additional safety net from preventable harm.

Known predictors of anticipated epidural difficulty include grade or ease of palpation of spinous process, presence of truncal versus lateral obesity with BMI >30 and abdominal girth, degree of exaggerated lumbar lordosis, pre-procedural ultrasound documentations of spinal anatomy and abnormalities.[8] The authors observed that besides BMI, technical difficulties result from variations of fat distribution that cause filling of "central valley" between the paraspinal muscles. These complexities that influence the level of difficulty in performing the procedure were not evident until the parturients were positioned to sit up for the epidural procedure. The distribution of adiposity did not relate to stratifications of patients by measurement of BMI. Factors that could be explored include body habitus pre-pregnancy, truncal or central obesity, and level of physical activity.[9]

Future prospective studies on comparison of rates of complication need to consider matching the level of expertise of proceduralists for the various ethnicities or when comparing the nationalities within the same ethnicities.[10] Decisions for offering opportunities for trainees (on who does the epidural) in "difficult epidurals" should be made from direct assessment of surface anatomy or sono-visualisation (present spinal ultrasound rate is <10%),[7] and by actual palpability of patients' lumbar spine.[11] This "anticipated difficulty" should be evaluated and established in person by the specialist or experienced midwife, and not through remotely accessed electronic records suggesting calculated high or normal BMI based on height or weight.[12] The study informs us of the safety of the existing structured training, with experienced nursing-supervision and escalation processes for specialist support in high-risk complex procedures, such as obstetric labour epidurals. The current study showed that the rates of complications and procedural concerns were comparable to global data on incidence of events (12.2%) where proficiency-based training progression and validation of readiness of trainees were ascertained.[13] The current system of structured introduction to complex clinical procedures, with guided specialist supervision for labour epidural analgesia and monitoring by experienced midwives, seems to be a safe practice and is commendable. Further prospective studies stratified by level of clinical expertise are needed to establish more concrete associations among anatomical variations, ethnicities and nationalities.

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Balakrishnan Ashokka [1,2]*MHPE*, Deepika Arora [3]*MD*, Shrividya Niranjan Kumar [4]*MD*, Rachel Chin [1]*MBBS*, Rajesh Kannan [1]*FFARCSI*, Bryan Ng [1]*FRCA*, May-Han Loh [1,2]*MMed*

[1] Department of Anaesthesia, National University Health System, Singapore
[2] National University of Singapore, Singapore
[3] Department of Anaesthesia, Newham Hospital, NHS Trust, London, UK
[4] Department of Anaesthesia, St Michael's Hospital, Ontario, Canada

Correspondence: Dr Balakrishnan Ashokka, Department of Anaesthesia, National University Hospital, Level 3 Main Building, 5 Lower Kent Ridge Road, Singapore 119074.
Email: ashokkab@gmail.com

LETTER TO THE EDITOR

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Pressure injuries related to N95 respirator masks among healthcare workers during the COVID-19 pandemic

Dear Editor,

The coronavirus disease 2019 (COVID-19) pandemic outbreak, which started in 2019, has affected millions of patients globally.[1] Singapore is not spared, being one of the first countries to import COVID-19 cases from China.[2] Nosocomial transmission of SARS-CoV-2 had been reported in various cohort studies of healthcare workers (HCWs), highlighting the importance of effective hospital infection control policies to mitigate risk.[3] In the process of protecting oneself from the SARS-CoV-2 infection, many of our HCWs suffered from skin issues ranging from pressure injuries to other skin-related lesions. While most existing literature surrounding pressure injuries is centred around patients, literature on pressure injuries in HCWs from personal protective equipment (PPE), though scarce, is rapidly emerging as the pandemic continues. A study conducted during the 2013 severe acute respiratory syndrome (SARS) outbreak in Singapore reported more than 50% adverse skin reactions resulting from PPE.[4]

The aim of our study is to examine the cross-sectional prevalence of pressure-related injuries among HCWs as a result of N95 masks in a tertiary healthcare institution during the COVID-19 pandemic.

An online questionnaire was designed to include all HCWs (doctors, nurses, allied health workers and ancillary staff) who were actively involved in patient care since the start of the COVID-19 pandemic in Singapore. Participation in this survey was optional and voluntary (see Supplementary Materials Appendix 1 in the online version of this article). The questionnaire was disseminated via Survey Monkey, an online survey platform (Momentive Inc, San Mateo, US) and was available for a duration of 3 weeks between July and August 2020. At the time of survey, N95 masks used at our institution were the 3M 8210, 3M 1860, 3M 1860S, 3M 8110S and 3M 1870+. The definition of pressure injury was defined using the standard guidelines from the National Pressure Injury Advisory Panel.[4]

Relevant data were collected and analysis using SPSS Statistics software version 24 (IBM Corp, Armonk, US). Univariate analysis was done using t-test for normally distributed continuous variables and chi-square test for categorical variables. Spearman's rank-order correlation (ρ) was used for ordinal variables. Multivariate analysis was performed using binary logistic regression. *P* value of ≤0.05 was considered to be statistically significant. Ethics review and approval were obtained from the National Healthgroup Domain Specific Review Board.

Of approximately 2,500 HCWs within our institution, 851 replied to our survey, giving a response rate of 34%. The demographics of our survey population is described in Appendix 2 (see Supplementary Materials Appendix 2 Table S1 in the online version of this article).

Of the 621 respondents who wore N95 masks daily at work during the pandemic, 394 (63.4%) answered "yes" to having had any pressure-related injuries as a result of their N95 masks (46.3% of the total surveyed population) (Appendix 2 Table S2).

A higher total average time of wearing the N95 mask correlates with a significantly higher risk of pressure injury (ρ=0.229, *P*<0.001, Appendix 2 Table S3). Also, the corresponding trend of a higher average time of wearing the N95 mask before "taking a break" also resulted in a significantly higher risk of pressure-related injury (ρ=0.140, *P*=0.001) (Appendix 2 Table S3).

Multivariate analyses showed that with the exception of 3M 1870+, there was a higher odd ratio of pressure injury when using the rest of the surveyed mask models (Appendix 2 Table S4).

Many of our respondents attempted self-management strategies including the use of emollients and prophylactic dressings (i.e. foam dressing, hydrocolloid and gauze) as a layer of cushioning over areas of high pressure such as bony prominences. A smaller number of respondents (29/208, 13.9%) shared that a change in N95 mask model to 3M 1870+ had helped to reduce or eliminate their pressure injury. Thankfully, most of our respondents (162/208, 77.9%) reported resolution with self-treatment.

Prior to the COVID-19 pandemic, the issue of pressure injury among HCWs was hardly mentioned in the literature. The prevalence of pressure injury from N95 respirator masks in our surveyed population was considerably high at 63.4%. Other similar studies have reported prevalence of skin-related problems from PPE ranging from over 50% up to 97%.[4,6,7] In addition, our results showed that increased total time of having

worn the N95 masks per day and increased duration of N95 mask usage between break times do significantly increase the risk of developing pressure injury; these findings are similar to other studies reported in literature.[8]

Current treatment strategies include regular moisturisers and/or barrier film wipes prior to N95 mask usage; and the use of prophylactic dressings between the N95 mask and the skin including thin hydrocolloid, silicone-based or foam dressings.[5,8-11] Some of these recommended management strategies are summarised in Table 1.

During the ongoing COVID-19 pandemic, the preventive strategies would be to focus on modifiable factors including care for the individual HCW and changes to the environment and working schedule. By sharing this information, we seek to create awareness and education on prevention of pressure injuries as part of mask-fitting exercises; adjust work environment and scheduling for HCWs who require prolonged N95 mask usage; and influence procurement of N95 masks models by taking staff comfort into key consideration.

The effect of increased awareness and education of pressure injury prevention from N95 respirator masks goes beyond the physical injury of the skin. While a mask-fit test is important to ensure a good mask seal, the act of over-tightening one's PPE will result in additional discomfort and eventual skin damage from pressure, besides not conferring any additional protective benefit.[7] Providing our HCWs with the knowledge surrounding prevention of pressure injuries would empower our staff and thus increase their resilience during a pandemic.[10]

To conclude, our survey showed a prevalence of pressure injury due to N95 masks usage at 63.4%. Risk factors for N95 mask-related pressure injury include high total average time of N95 respiratory mask use and longer durations of N95 mask use before "taking a break". Follow-up studies are needed to determine the effectiveness of preventive strategies and prophylactic dressings in reducing the prevalence of N95 mask-related pressure injuries in HCWs.

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Chong Han Pek [1]*FAMS (Plastic Surgery)*,
Yuan Kong [1]*MD*, Guey Fong Chin [2]*MHA*,
De Xin Zheng [3]*Adv Dip Nursing*,
Hin Kiaw Mary Chan [3] *BSc*,
Mansha Hari Khemlani [4]*FHKAM (Medicine)*

[1] Plastic, Reconstructive and Aesthetic Surgery Service, Department of Surgery, Khoo Teck Puat Hospital, Singapore
[2] Department of Nursing Administration, Khoo Teck Puat Hospital, Singapore
[3] Inpatient Wards, Department of Nursing, Khoo Teck Puat Hospital, Singapore
[4] Palliative and Supportive Care Services, Department of Geriatric Medicine, Khoo Teck Puat Hospital, Singapore

Correspondence: Dr Chong Han Pek, Plastic, Reconstructive and Aesthetic Surgery Service, Department of Surgery, Khoo Teck Puat Hospital, 90 Yishun Central, Singapore 768828.
Email: Pek.chong.han@ktph.com.sg

LETTER TO THE EDITOR

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Patterns and predictors of sound levels in hospital rooms

Dear Editor,

Excessive sound levels in the hospital can impair the work performance of healthcare professionals and affect patient well-being.[1] Previous studies have also linked excessive sound levels with sleep disturbances and cardiovascular morbidity.[2] While there have been data published regarding noise levels in the intensive care unit (ICU),[3] it is unclear whether there are differences in sound levels between ICUs and general wards (GWs). We sought to compare the patterns and predictors of sound levels in ICUs and GWs. We hypothesised that sound levels would be higher in ICUs than in GWs, and that sound levels in ICUs and GWs would be associated with patient-related equipment sources and non-equipment sources, respectively.[4]

We measured sound levels in 4 wards in 4 GWs and 3 ICUs, all with single bedrooms, at the National University Hospital, Singapore. The investigator was tasked to stand in the room for 1 minute every hour, and performed measurements sequentially from room to room without delay. Six days (3 weekdays and 3 weekends) of 24 hours each in June 2018 were evaluated. Paired average and peak sound levels inside each room were measured 1m away from the head of bed and for over 1 min hourly, via mobile phone apps (Decibel Ultra [Patrick Schaefer] for iOS [Cisco Systems Inc, San Jose, US] and Sound Meter [Abc Apps] for Android [Google LLC, Mountain View, US]).[5] Sound levels were measured with fast, A-weighting. Usual timings of doctor's ward rounds were from 1800h to 1000h, while nursing shift changes occurred at 0730h, 1600h and 2100h. As no patient data were collected, the need for ethics review was waived (approval number DSRB/2018/00460).

Multilevel mixed-effects linear regression, with sound level measurements nested within rooms nested within wards, fit by maximum likelihood, was used. In-room variables were analysed as time-varying covariates, and included presence of mechanical ventilation, non-invasive mechanical ventilation, supplemental oxygen devices, suction devices, nebulisers, medication pumps, feeding pumps, radio, television, vital signs monitor, active alarms, staff and family members.

We studied 10,894 pairs of average and peak sound readings (4,724 pairs in ICUs, 6,170 pairs in GWs). Between GWs and ICUs, no significant differences were found for average sound level (mean 48.5dB±standard deviation 10.8dB versus 51.6±6.0dB, P=0.224) and peak sound level (62.3±11.9dB vs 62.3±7.6dB, P=0.978). Peak sounds of >80dB were recorded every hour of the day, with proportion of peak sounds >90dB of 0.53% and proportion of peak sounds >100dB of 0.06%. Average sound level did not differ significantly between day (0700h–1859h) and night (1900h–0659h) (49.66±9.38dB vs 49.70±9.37dB, P=0.212), though peak sound level was higher during the day than at night (62.9±10.5dB vs 61.5±10.3dB, P<0.001). Both average sound level (50.2±8.9dB vs 49.2±9.9dB, P<0.001) and peak sound level (62.4±9.8 vs 62.2±11.1dB, P=0.014) were higher during weekdays (Monday–Friday, 0800h–0800h the next day) than weekends (Saturday 0800h–Sunday 0800h).

In the ICU, mechanical ventilation and presence of family members were associated with increased sound levels, while supplemental oxygen and medication pump use were associated with decreased sound levels (Table 1). In the GWs, presence of staff members and family members were associated with increased sound levels, while vital signs monitor use was associated with decreased sound levels. In both GWs and ICUs, nebuliser use, alarms and radio/television were associated with increased sound levels.

Contrary to our hypotheses, we found that peak and average sound levels did not differ between GWs and ICUs, while sound levels in both GWs and ICUs were affected by equipment-related and non-equipment-related sources. Average and peak sound levels in both GWs and ICUs exceeded the World Health Organization's recommended night noise level (40dB).[6] These are comparable to previously published data from other units.[7] Although significant, there was only a marginal drop of peak sound level (~1dB) from day to night, and marginal drops of average (~1dB) and peak (~0.5dB) sound levels from weekdays to weekends.

Strengths of our study include the detailed 24-hour data for weekdays and weekends. However, only 1 hospital was studied, which limits generalisability. Sound levels measured using mobile phones are also not as accurate as environmental monitoring equipment. A bias in measurement remains when a human is visibly recording sounds, as it is very likely that people within the area would modify their behaviour following awareness of being observed. Thus, it is likely that sound levels are higher than reported, which highlights the need for average and peak sound levels in both GWs and ICUs to be managed at all times, especially using

Table 1. Association of environmental factors on sound levels in hospital rooms

Environmental factors	Change of average sound level (dB) (95% CI)		Change of peak sound level (dB) (95% CI)	
	GW	ICU	GW	ICU
Mechanical ventilation	NA	-0.13 (-0.98–0.73)	NA	1.81* (0.58–3.03)
Non-invasive ventilation	NA	1.35 (-1.40–4.10)	NA	1.37 (-2.56–5.30)
Supplemental oxygen use	0.67 (-0.44–1.78)	-4.83* (-5.82–-3.85)	0.31 (-0.86–1.48)	1.14 (-0.26–2.54)
Suction device use	-6.29 (-19.84–7.25)	-0.93 (-2.03–0.19)	-10.98 (-25.40–3.45)	-0.27 (-1.84–1.30)
Nebuliser use	9.01* (1.15–16.88)	2.42* (0.35–4.48)	6.86 (-1.51–15.23)	-0.19 (-3.15–2.76)
Medication pump	-0.18 (-0.96–0.60)	-2.50* (-3.37–-1.63)	-0.28 (-1.11–0.55)	-3.79* (-5.03–-2.55)
Feeding pump	4.03 (-3.22–11.26)	0.41 (-0.49–1.31)	5.24 (-2.47–12.94)	-0.41 (-1.68–0.87)
Radio/television	0.65* (0.04–1.27)	2.13* (1.31–2.96)	1.60* (0.13–3.10)	2.04* (0.87–3.22)
Vital signs monitor	-1.98* (-3.25–-0.70)	0.79 (-0.28–1.86)	-1.93* (-3.27–-0.58)	-0.33 (-1.84–1.19)
Alarms	1.78* (0.37–3.18)	0.87* (0.09–1.66)	1.61* (0.12–3.10)	0.54 (-0.59–1.66)
Presence of family	-0.80 (-1.73–0.12)	1.87* (1.08–2.65)	1.33* (0.35–2.31)	1.86* (0.74–2.98)
Presence of staff	2.12* (1.31–2.94)	0.57 (-0.27–1.40)	5.23* (4.36–6.09)	-0.17 (-1.35–1.01)

CI: confidence interval; dB: decibel; GW: general ward; ICU: intensive care unit; NA: not applicable
* $P<0.05$: using multilevel mixed-effects linear regression, with sound level measurements nested within rooms nested within wards, fit by maximum likelihood

policies that simultaneously target multiple modifiable environmental factors to lower sound levels.[8] Our results also support guideline-recommended protocols that reduce noise exposure and promote sleep for critically ill patients.[9]

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Wei Yang Lim [1]*MRCP (UK)*, Han Tun Aung [2]*MBBS*, Kay Choong See [1]*FRCP (Edin)*

[1] Division of Respiratory and Critical Care Medicine, Department of Medicine, National University Hospital, Singapore
[2] School of Health Sciences, Ngee Ann Polytechnic, Singapore

Correspondence: Dr Kay Choong See, Division of Respiratory and Critical Care Medicine, Department of Medicine, National University Hospital, 1E Kent Ridge Road, NUHS Tower Block Level 10, Singapore 119228.
Email: mdcskc@nus.edu.sg

LETTER TO THE EDITOR

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Stress among emergency medicine residents during the COVID-19 pandemic: A qualitative study

Dear Editor,

The COVID-19 pandemic has disrupted medical education[1,2] and distressed clinicians.[3,4] Understanding the impact of this pandemic on emergency medicine (EM) residents' experience of stress will allow for more effective interventions to aid residents, while reducing attrition and its impact on pandemic response.

We present our qualitative study, guided by a theoretical framework underpinned by empirical evidence, which explicitly explored residents' experiences of stress during the pandemic, important and modifiable underlying factors, and how this can guide prioritisation of limited resources to aid residents. Ethics approval was obtained (DSRB reference number 2020/00523).

We framed our study using the Lazarus and Folkman transactional model of stress,[5] given its strong empirical foundations. In this model, stress is a relationship between the individual and the environment that is cognitively appraised as exceeding the individual's resources and threatening well-being.

Cognitive appraisal comprises 2 parts. Primary appraisal determines what is at stake, i.e. whether it is irrelevant, beneficial or threatening to the individual. Commitments influence primary appraisal, with deeper commitments increasing potential threat and driving coping efforts. Secondary appraisal evaluates coping options based on availability, and ability to accomplish the intended outcome and apply them effectively. Coping is the process of managing the demands of the person-environment relationship and the emotions generated.

The study was conducted according to the COnsolidated criteria for REporting Qualitative research (COREQ) checklist[6] and a phenomenological paradigm. Purposive sampling was employed to ensure representation across sites and levels of training. Sampling was deemed complete when thematic saturation was achieved, i.e. no new themes emerged. There were 92 EM residents in Singapore during the study period (October–November 2020); all were eligible and invited for recruitment via email. Twenty-six residents were recruited, and 4 focus group discussions (FGDs) were conducted. FGDs lasted 49–65 minutes. No residents dropped out after recruitment. Written informed consent was obtained from all participants. Participation was voluntary and none received compensation.

FGDs were conducted by 2 study team members and in groups of 5–8 participants, through video calls at home. One study team member was the primary moderator, and the other was an observer and notetaker. To foster psychological safety, the residents were grouped according to level of training, with FGD moderators from a different resident training site. FGDs were semi-structured with an interview guide derived from consensus among the study team, guided by literature review. Questions explored participants' experiences of stress in general during the pandemic, cognitive appraisals and coping strategies. Audio of the interviews were recorded and transcribed by the primary moderator.

Each transcript was first analysed using open coding by study team members who worked in pairs. As themes emerged from analysis of the first 2 transcripts, a coding template that included major themes was produced based on consensus among the study team, and applied to all transcripts. Further discussion refined themes to encompass the data as fully as possible. Transcripts and codes were returned for member checking by the participants.

Three major themes emerged and are described with illustrative quotes in Table 1.

Theme 1: **Stress appraisal was influenced by adequacy of resources that residents valued**. Such resources included information about COVID-19, continued exposure to non-pandemic cases for learning, manpower commensurate with workload, isolation facilities and workflows, personal protective equipment and job security. When these resources were plentiful, gratitude was induced. The pandemic was a unique learning opportunity, but with limited value that eroded over time.

Theme 2: Commitments influence cognitive appraisal. The pandemic was an opportunity to fulfill residents' commitment to professional identity. This was reinforced by senior staff role modelling commitment to colleagues. Commitments to next of kin contributed to stress and feelings of isolation for residents who had migrated for work and could not return due to lockdowns.

Theme 3: **Effectiveness of individual and system coping strategies.** Online learning was appraised as convenient, though sometimes ineffective due to difficulty in maintaining attention, and inability to

Table 1. Themes, sub-themes and quotes illustrating the residents' experiences

Theme	Sub-theme	Quotes
Stress appraisal is influenced by the adequacy of resources valued by residents	Information about the disease	Participant 2-4: "Stressful to work in seeing COVID-19 cases, because at that period of time, we don't know how deadly this disease is, how fast it spreads."
	Continued exposure to non-pandemic cases for learning	Participant 2-3: "…taken away from our main ED (emergency department) practice and we are not able to see the general population of cases; instead we are seeing foreign workers or the URTIs (upper respiratory tract infections) that are referred from the GPs (general practitioners) and I would feel that it affects our learning because we only know how to clear URTI cases now." Participant 1-3: "When you are in the whole COVID situation, no one really thinks about training that much anymore. You just deal with the load."
	Procedural learning opportunities	Participant 4-4: "Hoping for greater yield of procedures, but…less opportunities for chest drains because less patients coming in with pleural effusions."
	Manpower commensurate with workload	Participant 1-3: "When I was at the dirty ICU (intensive care unit), our admission rate was 3 times of the clean team, but at the same time, the ratio of the staffing is the same, one to one. No one asked us, 'Are you all overloaded? Are you all ok?'"
	Isolation workflows and facilities	Participant 4-6: "In some other institution(s), I know that they have special pathway(s) for them to transfer the patient from the ED to the ICU… in my hospital we don't have this… they will definitely go through the general walkway and might have some contact with the rest of the patient(s)." Participant 2-4: "What we don't want is getting a call few hours later or the next morning, 'you just exposed 6 healthy patients to 1 COVID-19 patient.'"
	Personal protective equipment (PPE) and job security	Participant 4-1: "I have friends in (another country)… They are telling me that they see COVID suspects just with a surgical mask... The resources we have are really great compared to what my friends and siblings have out there in different countries." Participant 1-5: "There were so many people out there who either lost their jobs or (who were) stuck at home. They were essentially almost like locked up at home because everybody cannot go out, while I still can go to my job daily."
	Pandemic as a learning opportunity	Participant 3-4: "A very wonderful opportunity for the ED people to learn. How many of us see a pandemic once in our lifetime, to actually see it run on the ground?"
	Deteriorating appraisal of the pandemic over time	Participant 2-5: "In the first 1 or 2 months, everyone is very fired up… so initially we didn't really feel the pain... We started to feel it around the third month, because we lose all this training, then we never get smarter, we just keep seeing COVID patients."
Commitments influence cognitive appraisal	Opportunity to fulfill commitment to professional identity	Participant 1-1: "This is our job. We signed up for this. As A&E (accident and emergency) people, we are frontline for this. I don't think any of us would have chosen otherwise."
	Inspired by senior staff role modelling commitment to colleagues	Participant 1-3: "If you see certain seniors, willing to be busy and getting down to do the dirty shift, or volunteer to do more of the dirty shifts with you, then you are more inspired… What's most motivating is the feeling that everyone is doing this together."
	Threat arising from commitment to connections with next of kin	Participant 4-5: "Because I'm not a local, I've not actually been home for a year… I have times that I dearly miss my family but unfortunately I can't do much about it."
Effectiveness of individual and system coping strategies	Online learning as beneficial	Participant 4-1: "Definitely very convenient… I like my big screen in my room, having my own coffee… saves me a lot of travelling time."
	Drawbacks of online learning	Participant 3-1: "I personally prefer physical classroom or auditorium teaching. I find it hard to concentrate on online Zoom teaching." Participant 3-3: "Some things cannot be replaced by the online teaching like the procedural skills and simulation."
	Importance of self-regulation: time management	Participant 4-6: "For those people who are not compliant, this will be a bit tough because there is a lack of supervision...there're pros and cons… If the resident can manage themselves quite well, time management is good, I think it's very good for learning."

Table 1. Themes, sub-themes and quotes illustrating the residents' experiences (Cont'd)

Theme	Sub-theme	Quotes
	Importance of self-regulation: strategic planning and independently seeking out teachers who had adapted well to the new educational landscape	Participant 1-4: "Those who did very well, they approached us about how to go about doing the tutorials, how to improve the tutorials… I just prioritised the tutors I felt were optimising the Zoom tutorial sessions and contributing the most to help me."
	Quicker resumption of education through drawer plans	Participant 2-1: "The purpose of having drawer plans is so that we can have a quicker response if it ever happens again...so that they don't lose their training time."
	Communication between faculty and residents aided coping	Participant 3-5: "…received a call from my PD (programme director)…they would try their best to help and we can talk to them anytime we have a problem."
	Drawing strength from connections with family and friends	Participant 1-1: "It's really helpful to have a good work family or friends around so that was a supporting factor. Especially family members."
	Value of safe social interaction with colleagues	Participant 2-3: "I actually enjoyed and looked forward to going to work because that was the most social interaction I probably had physically, and it was only possible because we were all in PPE and we don't need to stay like 5m away from each other and then we can actually sit around the seniors' counter and talk like normal." (The rest of the group laughs.) Participant 4-6: "Our residents will still do exercise together…in our meeting, but with social distancing. So, we HIIT (high intensity interval training) together, do cardio together (laughs)."

replace simulation or procedural skills training. Residents recognised the need for self-regulation skills, such as strategic planning and time management to cope with the new educational landscape, characterised by greater learner independence. Communication with faculty members and loved ones, and social interaction at work, mitigated feelings of isolation.

Our findings suggest the following targets for intervention to address stress among residents:

1. Optimising use of limited resources by prioritising the most impactful, i.e. those valued by residents. There is potential to transform stress into gratitude, which demonstrates a wider extent of impact that resource adequacy has compared to previous studies.[3,4]
2. A deliberately planned balance between pandemic and non-pandemic case exposure, to extract learning value from the pandemic, while maintaining sufficient exposure to business-as-usual cases for core clinical training.
3. Role modelling by senior clinicians, to strengthen commitment to professional identity and colleagues as a protective factor.
4. Deliberately fostering social interactions in a physically safe manner between residents, colleagues and loved ones.
5. Improving the effectiveness of online learning through thoughtful implementation based on established principles,[7] since the future of medical education has likely been permanently altered,[8] with online learning now increasingly integral. However, as online learning is an inadequate modality in some contexts (e.g. for procedural skills), new ways to safely conduct face-to-face and workplace-based training should be explored.
6. Fostering self-regulation skills,[9] including but not limited to those highlighted by the participants in our study.

As we were limited to a single country's EM residency programmes, our findings may not be generalisable to other settings with a different disease burden. Interestingly, stigmatisation of healthcare workers was not a prominent theme in this study, in contrast to literature.[10] Further studies may examine the reasons for this, and whether the factors identified in our cohort are generalisable across different stressful situations, and even across specialties. Measurable effectiveness of the interventions that targeted stressors would also help to ascertain our presented strategies as proven stress management measures for residents.

In conclusion, leadership in residency programmes can focus on targets identified in our study to mitigate stress among residents during a pandemic.

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Matthew Jian Wen Low [1]*MBBS (Hons)*, Chaoyan Dong [2]*PhD*, Daniel Yong Jing Quek [3]*MMed*, Jian Hui Ng [3]*MB Bch*, Han Nee Gan [4]*MRCSEd*, Thian Phey Lau [1]*MCEM*, Jen Heng Pek [5]*MCEM*

[1] Emergency Medicine Department, National University Hospital, Singapore
[2] Education Office, Sengkang General Hospital, Singapore
[3] Emergency Department, Tan Tock Seng Hospital, Singapore
[4] Accident and Emergency Department, Changi General Hospital, Singapore
[5] Department of Emergency Medicine, Sengkang General Hospital, Singapore

Correspondence: Dr Matthew Jian Wen Low, Emergency Medicine Department, National University Hospital, Level 4, National University Centre for Oral Health, 9 Lower Kent Ridge Road, Singapore 119085.
Email: matthew_low@nuhs.edu.sg

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An intensely pruritic disseminated skin eruption

A 64-year-old man presented to the dermatology outpatient clinic with a 4-month history of pruritic papules. He had a significant medical history of thyrotoxicosis, which was diagnosed 1 year prior and well controlled on carbimazole. He had no history of dyslipidaemia or underlying malignancy. The cutaneous eruption had first started on his abdomen, over his tattoo site. The tattoo was obtained 40 years prior, and he denied application of any topical medicaments over the area. The papules had been gradually expanding to include the rest of his chest, abdomen and back. Physical examination revealed multiple erythematous papules on his trunk that were moderately profuse. Some lesions were distributed in an annular configuration over his tattoo-naive chest and back, and the lesions did not correspond geographically to the pattern of his tattoo (Fig. 1).

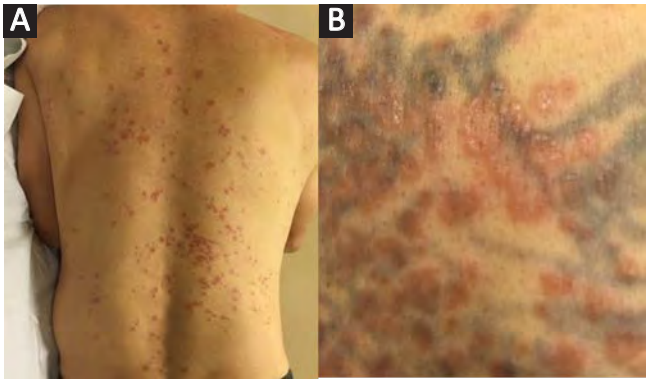

Fig. 1. Lesions distributed over the patient's (A) back and (B) abdomen.

Histological findings, diagnosis, treatment and progress. A biopsy of the papules revealed non-caseating granulomas, with focal necrobiosis and no giant cell inclusions (Fig. 2). Infective stains (periodic acid-Schiff stain, Ziehl-Neelsen stain, Grocott's methenamine silver stain and Wade-Fite stain) were negative. Dermal mucin was seen on Alcian blue staining. Other screening laboratory investigations for diabetes mellitus, hyperlipidaemia and human immunodeficiency virus were negative.

What is the most likely diagnosis?

A. Tattoo granuloma
B. Eruptive xanthomas
C. Molluscum contagiosum
D. Disseminated granuloma annulare
E. Cutaneous papular sarcoidosis

A clinical diagnosis of disseminated granuloma annulare (DGA) was made. The patient was initially treated with potent topical steroids, such as clobetasol propionate cream and various antihistamines, without any improvement. After discussion with the patient, he was started on thrice-weekly narrow band ultraviolet B (NBUVB) phototherapy with a regime based on his skin phototype, starting from 400mJ/cm^2. He demonstrated good temporal response to therapy with symptomatic reduction in pruritus, reduction in erythema and induration of the papules within the first month of phototherapy, and subsequent decrease in total body surface area affected. He tolerated the treatment well and was stepped down to twice-weekly phototherapy sessions after 3 months, and eventually stopped on resolution of his lesions at 6 months. His cumulative irradiation dose was 28.53J/cm^2 over a total of 44 sessions. After cessation of NBUVB, he was followed up in the clinic with review sessions. He remained in remission with no further recurrence.

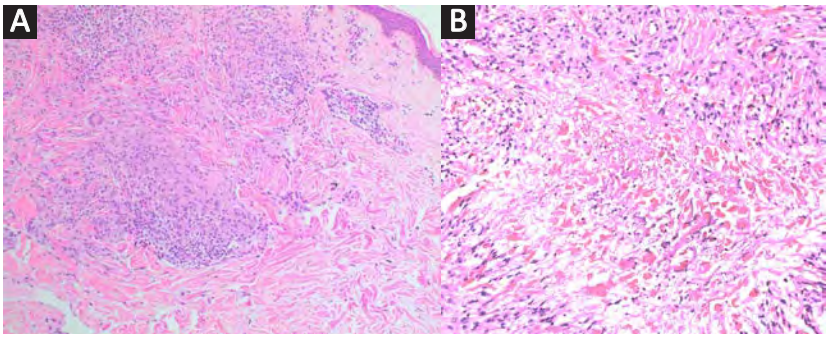

Fig. 2. (A) Non-caseating granulomas at 100x magnification on haematoxylin and eosin stain. (B) Focal necrobiosis and palisading granulomas at 400x magnification.

Answer: D

Table 1. Summary of the patient's condition, clinical morphology and histology

Condition	Clinical morphology	Histology
Tattoo granuloma	Papules and nodules occurring only at the site of a tattoo	Granulomas with pigment-laden macrophages
Eruptive xanthomas	Yellow to skin-coloured papules, mostly on extensor surfaces	Foam cells and Touton giant cells in the dermis
Molluscum contagiosum	Pearly umbilicated papules	Infundibular hyperplasia and papillomatosis with central umbilication
Disseminated granuloma annulare	Widespread erythematous skin-coloured papules, usually symmetrical and grouped	Dermal palisading granulomas with collagen degeneration, lymphocytic infiltrates and increased dermal mucin
Cutaneous papular sarcoidosis	Erythematous skin-coloured dermal papules	"Naked" epithelioid granulomas

Discussion. DGA is uncommon, and unlike localised granuloma annulare that spontaneously resolves, it is particularly difficult to treat. While the underlying aetiology of DGA remains unknown, Mempel et al. postulated a T-cell-mediated immune response involving cytokines such as interleukin-2 (IL-2) to be the main drivers, with breakdown of matrix, elastic tissue and collagen by elastases, collagenases and metalloproteinases.[1]

DGA typically presents with groups of skin-coloured or erythematous dermal papules, and patients are commonly disturbed by its cosmetically obvious and widespread appearance, and unbearable pruritus. It is characterised by granulomas with lymphohistiocytic infiltrates on histology.

Treatment is guided by expert opinion and existing literature, which remains mostly limited to case reports.[2-6] Phototherapy has immunomodulatory effects, and has been proposed to play a role in the inhibition of T-lymphocytes, which are key in the pathogenesis of DGA.[3] In addition, phototherapy is an advantageous modality over other systemic therapies such as isotretinoin, biologics or fumaric acid esters due to its relatively safer side effect profile.[3] NBUVB has also been found superior to both broadband ultraviolet B and ultraviolet A in the suppression of cytokine and lymphocyte proliferation—the suppression of which has been proposed to thwart granuloma formation in DGA.[5,6] The role of NBUVB in the treatment of DGA in our context has also been similarly supported by previous case reports.[6]

Koebnerisation is a phenomenon that can be seen in both cutaneous sarcoidosis and tattoo granulomas, when lesions occur at previous sites of cutaneous injury. However, our patient's rash was not solely confined to the tattoo sites, and there were no temporal sequelae (Table 1).

Although eruptive xanthomas can also present as dermal papules, they are characteristically yellow in colour, and tend to present over the extensor surfaces, such as the elbows, knees and shoulders.

Tattoo granulomas are hypersensitivity reactions to the pigment used in tattoos. The condition typically manifests with granuloma formation as opposed to epidermal spongiosis, which is typically seen in contact dermatitis on histology.

Molluscum contagiosum, on the other hand, is a cutaneous infection by the poxvirus. It presents with distinctive waxy papules with central umbilicated pits, and intracytoplasmic inclusion bodies with infundibular hyperplasia and papillomatosis on histology.

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Laura LY Hui [1]*MCRP*, Michelle MF Chan [2]*FRCPath*, Shiu Ming Pang [1,3]*FRCP (London)*

[1] Department of Dermatology, Singapore General Hospital, Singapore
[2] Department of Anatomical Pathology, Singapore General Hospital, Singapore
[3] Duke-NUS Medical School, Singapore

Correspondence: Dr Laura LY Hui, Department of Dermatology, Singapore General Hospital, Outram Road, Block 6 Level 9, Singapore 169608.
Email: lauraahui@gmail.com

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Torsades de pointes in a woman presenting with syncope

A 57-year-old woman presented with first onset syncope, which was witnessed by her family members. It occurred in the middle of a conversation and lasted for 30 seconds, followed by spontaneous and prompt recovery. There was upward rolling of eyeballs with no witnessed tongue biting, jerking of limbs or urinary incontinence. There was no family history of sudden cardiac death or heart disease. She denied symptoms of chest pain, palpitation, dyspnoea, diaphoresis and fever. She was not taking any medication or over-the-counter supplements. In addition, there was no identifiable stressors preceding this syncopal episode.

On arrival to hospital, she was afebrile; her blood pressure was 145/89mmHg, with a heart rate of 40–70 beats per minute, respiratory rate of 16 breaths per min and oxygen saturation of 98% on room air. Initial electrocardiogram (ECG) revealed sinus bradycardia, premature ventricular complexes (PVC), prolonged QT interval (corrected QT [QTc] 600ms), and T inversions in leads aVL and V2–6 (Fig. 1A). Laboratory result revealed normal electrolytes (including potassium, magnesium and calcium), liver function, thyroid function and phaeochromocytoma panel. Her initial high-sensitive troponin level was 1,834ng/L and peaked at 3,737ng/L (normal range 0–18ng/L). Chest radiography showed no consolidation or pleural effusion. Her reverse transcription polymerase chain reaction for COVID-19 came back negative.

Coronary angiogram showed slow flow and mild coronary artery disease. Left ventriculogram revealed apical ballooning with hyperkinesia of the basal anterior and inferior walls (Fig. 1B). Immediate transthoracic echocardiogram (TTE) showed left ventricular ejection fraction (LVEF) of 35% with wall motion abnormalities (Figs. 1C and D).

During the cardiac catheterisation, patient developed recurrent episodes of torsades de pointes (TdP), and required electrical cardioversion (Fig. 2A). A temporary pacing wire (TPW) was inserted in view of recurrent TdP with a back-up pacing rate set at 80 beats per minute. Cardiac magnetic resonance imaging (CMR) was carried out to exclude reversible causes including myocarditis.

What do Figs. 1 and 2 demonstrate?

A. Arrhythmogenic right ventricular cardiomyopathy
B. Coronary artery dissection
C. Coronary vasospasm
D. Myocarditis
E. Takotsubo cardiomyopathy

CMR showed early oedema in the apex, consistent with diagnosis of takotsubo cardiomyopathy (TCM)

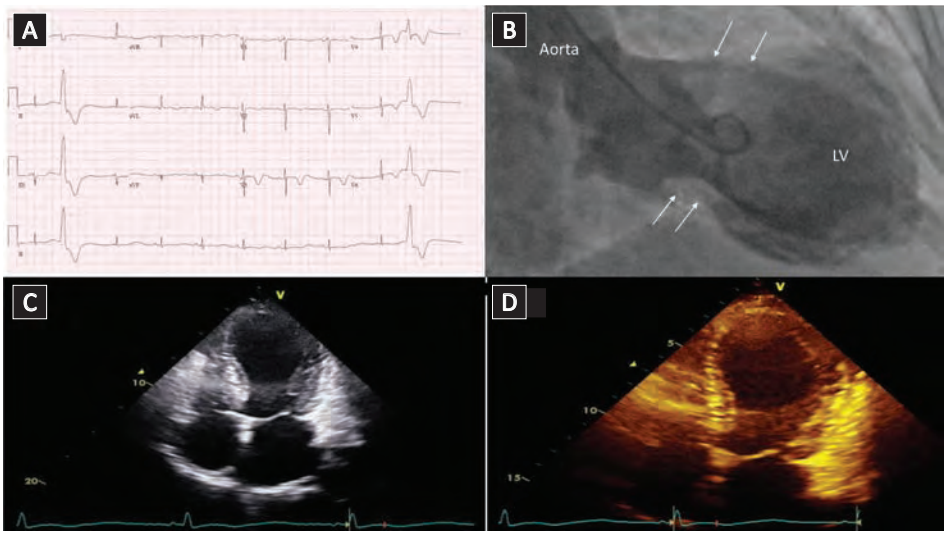

Fig. 1. (A) Initial electrocardiogram showing sinus bradycardia, prolonged QTc (600ms) and premature ventricular complexes. (B) Left ventriculogram showing hyperkinesia in the basal segment and akinetic apex (arrows). (C) and (D) Transthoracic echocardiogram showing hypercontractile in the basal segment.
QTc: corrected QT

Answer: E

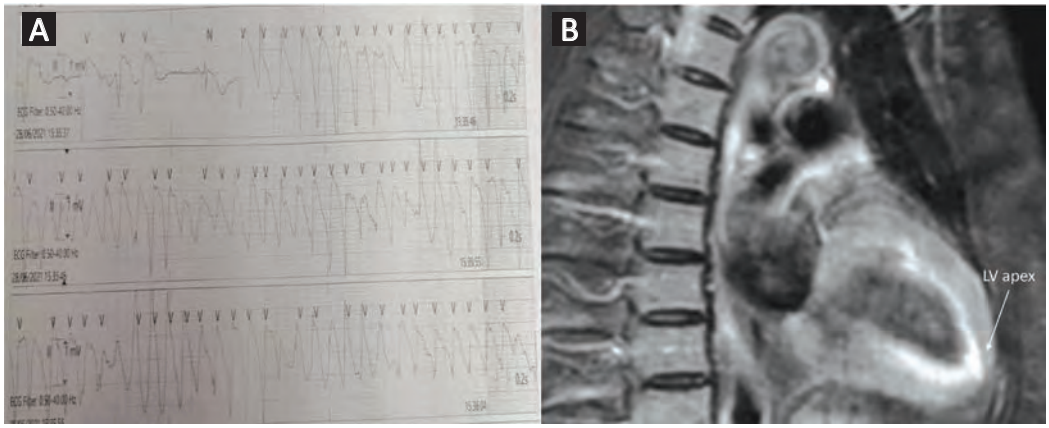

Fig. 2. (A) Telemetry revealing significant torsades de pointes. (B) Cardiac magnetic resonance imaging showing oedema, which is worst in the apical region.

(Fig. 2A). There was no evidence of late gadolinium enhancement or features of myocarditis on CMR.

The patient had regular 12-lead ECGs and her QTc remained lengthened at 500–600ms with frequent PVCs seen despite initiation of beta-blockers. Furthermore, when attempting to wean off TPW by reducing the pacing rate to 50bpm, the patient developed TdP. Decision was made for insertion of implantable cardioverter defibrillator (ICD) for secondary prevention. ICD was implanted on day 14 of hospitalisation. She was discharged well on bisoprolol, atorvastatin and aspirin. Subsequent TTE (2 months post-discharge) showed resolution of wall motion abnormalities with recovery of LVEF to 55%. A follow-up 12-lead ECG showed atrial paced rhythm with QTc of 456ms (Fig. 3). Device interrogation did not reveal any episode of ventricular arrhythmia.

Coronary artery dissection and vasospasm are key differential diagnoses to consider in this case. Thus, coronary angiogram remains the gold standard in evaluating coronary anatomy. However, the presentation was atypical as patients would usually complain of chest pain rather than syncope. Myocarditis needs to be excluded in the setting of raised troponin, wall motion abnormalities and patent coronaries. Lake Louise criteria placed a great emphasis on CMR as an imaging modality in diagnosing myocarditis. Arrhythmogenic right ventricular cardiomyopathy is less likely in the absence of right ventricular impairment and dilatation.

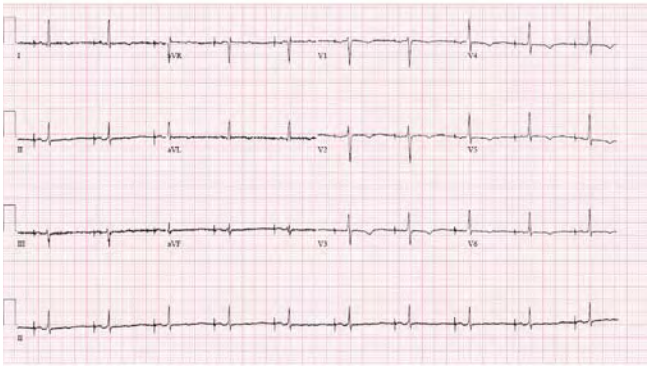

Fig. 3. Electrocardiograph revealing shortening of QTc (456ms) and atrial paced rhythm after implantation of implantable cardioverter defibrillator.

This case highlights the association of recurrent episodes of TdP from acquired long QTc syndrome and TCM. Investigation for prolonged QT interval remains challenging as this often involves multiple modalities with a wide range of differential diagnosis to entertain. Female and old age are the only non-modifiable predisposing factors for acquired long QT-syndrome (LQTS).[1] TCM, despite being a reversible form of cardiomyopathy, may not be benign as this patient presented with syncope with evidence of prolonged QT interval and required an ICD as secondary prevention. It is known that the risk of TdP escalates as QT interval increases.[2] Early afterdepolarisation-induced triggered activity in the setting of catecholamine excess has been postulated to increase TdP risk. Our patient presented with a substantially prolonged QT interval of 600ms, which had likely led to cardiogenic syncope from Tdp. The QT interval shortened to 456ms after recovery from TCM with no further ventricular arrhythmias detected. Reduction of QT interval (T_{peak}–T_{end}/QT ratio) dispersion are associated with recovery.[3]

TCM is a rare disorder characterised by transient, reversible left ventricular dysfunction commonly triggered by emotional or physical stress. The US Mayo Clinic criteria are widely adopted by cardiologists in an attempt to better describe the syndrome.[4] The association between TCM and acquired LQTS have been described in case reports.[5] However, life-

threatening arrhythmias (ventricular fibrillation or TdP) in this group of patients are extremely uncommon.

Emotional and physical stressors are recognised triggers for TCM. However, in approximately 30% of patients, TCM occurred without any evident trigger.[6] To note, emotional stress or lack of identifiable triggers is more common in women while physical stress leading to TCM is more common in men. There were no identifiable physical or emotional stressors in our index case. Singapore studies have demonstrated that TCM mainly affects post-menopausal women with recent trigger from a surge in catecholamines.[7,8]

Management of TCM remains largely supportive to sustain life and minimise complications until full recovery, which may take weeks. To date, there have been no randomised trials to define optimal treatment of TCM. The use of angiotensin-converting-enzyme inhibitors or angiotensin receptor blockers was associated with improved survival, though the usage of beta-blockers was not.[6] Temporary transvenous pacing should be considered in the acute setting if patient has TdP.[9] In this case, there were additional features suggestive of high-risk LQTS (post-TCM QTc >500ms, previous syncope and TdP), which necessitate the implantation of ICD.[10]

In conclusion, TCM should be recognised as one of the causes of acquired long QT syndrome, in addition to its associated risk of Tdp. There is still much to learn regarding the aetiology and underlying pathophysiology of TCM. Future studies including randomised trials are needed for optimal management of this condition.

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Shiun Woei Wong [1,2,3]*MRCP (UK)*, Shonda Ng [1]*MRCP (UK)*, Joo Hor Tan [1]*MRCP (UK)*

[1] Department of Cardiology, Tan Tock Seng Hospital, Singapore
[2] Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore
[3] Yong Loo Lin School of Medicine, National University of Singapore, Singapore

Correspondence: Dr Shiun Woei Wong, Department of Cardiology, Tan Tock Seng Hospital, 11 Jalan Tan Tock Seng, Singapore 308433.
Email: shiunwoei@gmail.com

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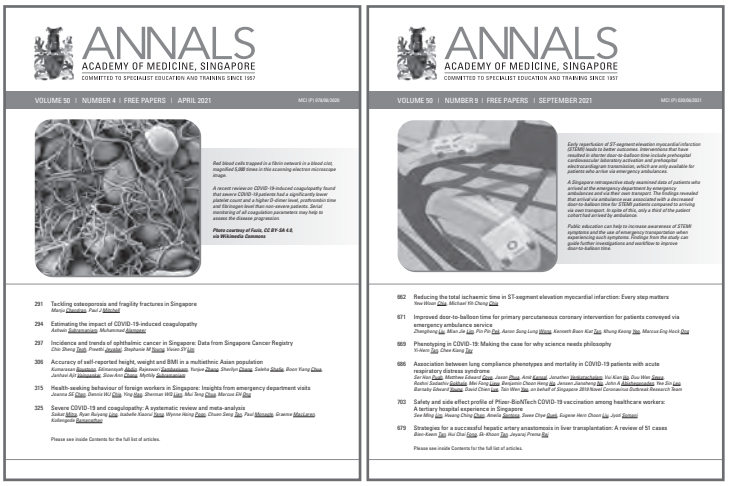

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