SCANDINAVIAN JOURNAL OF UROLOGY
2021, VOL. 55, NO. 1, 86–88
https://doi.org/10.1080/21681805.2020.1792978

LETTER TO THE EDITOR

Evidence-based medicine, the number 'three' and its multiples in urological clinical rules

Dear Editor,

Medical progress throughout centuries has been founded on careful observation, and its level of acceptance was based largely on the eminence of teaching physicians. It was not until the early 1990s that the term 'Evidence-Based Medicine' (EBM) was first used, and was defined as 'the conscientious, explicit, and judicious use of the current best evidence in making decisions about the care of individual patients' [1]. When applying this principle to our everyday urological practice, we have noticed that the number 'three' and its multiples (6, 9, 12, etc.) occurs quite often in diagnosis, management, and follow-up of patients, and most of the times with no explicit supporting high-quality evidence. This is also present in other medical specialties [2]. Our aim was to investigate the presence of the number three and its multiples in the urological daily practice, and to present any underlying supporting evidence.

Warm kidney ischemia is known to be '30 min' among urologists during partial nephrectomy and is based on a canine study in 1975. However, while Funahashi et al. [3] have shown that warm ischemia time in order to preserve kidney function is ideally $<$20 min, Parekh et al. [4] have concluded that a human kidney can tolerate 30–60 min of controlled clamp ischemia, and the ancient concept that 'every minute counts' is revoked. Moreover, the typical window of opportunity for surgical intervention in testicular torsion is thought to be '6 h' from onset of pain with a proved 90% salvage rate. However, a recent systematic review has demonstrated that survival of testis (1) can be much longer than 6 h 'that is commonly taught', and (2) is believed to be significant even after 24 h of testicular torsion [5].

While there is no consensus on the management of Acute Urinary Retention (AUR), the standard of care has evolved into doing a trial without a catheter (TWOC). A 3-day period of catheterization in addition to an α1-blocker is usually preferred by urologists, and a recent study confirmed that catheterization for $>$3 days is associated with a lower success rate of TWOC, a larger comorbidity and a higher rate of prolonged hospitalization due to adverse events [6].

This 'three-multiplicity' rule can be found in prostate, bladder, and kidney cancer management. The simplest illustration would be the follow-up schedule after surgery for these cancers, which is recommended at 3, 6, and 12 months postoperatively, every 6 months thereafter until 3 years, and then annually. This is endorsed by the international guidelines. However, for prostate cancer for example, Matsumoto et al. [7] have shown in a cohort of 1,010 patients that the optimal follow-up schedule can be done at 1, 2, 3, 4, 6 or 8 months after 1, 2 or 3 years, depending on the serum PSA value.

Speaking about prostate cancer, the number of prostatic biopsy cores follows also the rule of three. At first, sextant systematic biopsy was proposed, and then, it increased to 12 cores, a maximal number demonstrated to be sufficient. However, nomograms determining the number of core biopsies based on the patient age and prostate volume have been published and reported that this number can range from 6 to 12 [8]. Moreover, concerning duration of androgen deprivation therapy when combined with radiotherapy for prostate cancer, Bolla et al. [9] have shown that a duration of '6 months' is inferior to '3 years' without a clear explanation to the choice of duration; then, a duration of '18 months' was shown to be non-inferior to '36 months' [10]. We can also mention the 'trifecta' of prostate cancer survival combining cancer control, continence and maintenance of sexual potency.

When tackling bladder cancer, guidelines recommend a cystoscopy after 3 months (the most important prognosticator cystoscopy) of the transurethral resection of a bladder tumor, and then: 9 months later for low-risk Ta tumors if no disease found, and every 3 months for two years (24 months) and every 6 months thereafter until five years (60 months) for high-risk tumors (with no clear evidence in the literature supporting these recommendations). Moreover, concerning BCG cycles, when first described, 120 mg of BCG was repeated at weekly intervals for 6 weeks, and now guidelines recommend induction at 6 weeks and then maintenance using installations 3 times per week, at 3, 6, 12, 18, 24, 30 and 36 months. We should interestingly note that the standard BCG regimens were initially based on the number of bottles of medication that came in one package, in order to keep a single package for a single patient. Convincing evidence for the optimal number of induction instillations, frequency and duration of maintenance therapy is lacking until now, and due to the countless number of possible combinations, studies are unlikely ever to be realized.

We can also mention the symptomatic 'triad' of kidney cancer. Although a rare finding (6–10%) in patients nowadays, the classic triad of flank pain, visible hematuria, and palpable abdominal mass is still discussed and correlates with aggressive histology and advanced disease based on low level of evidence studies. The 'triad' concept is present in the semiology and diagnosis of diseases in almost all medical specialties.

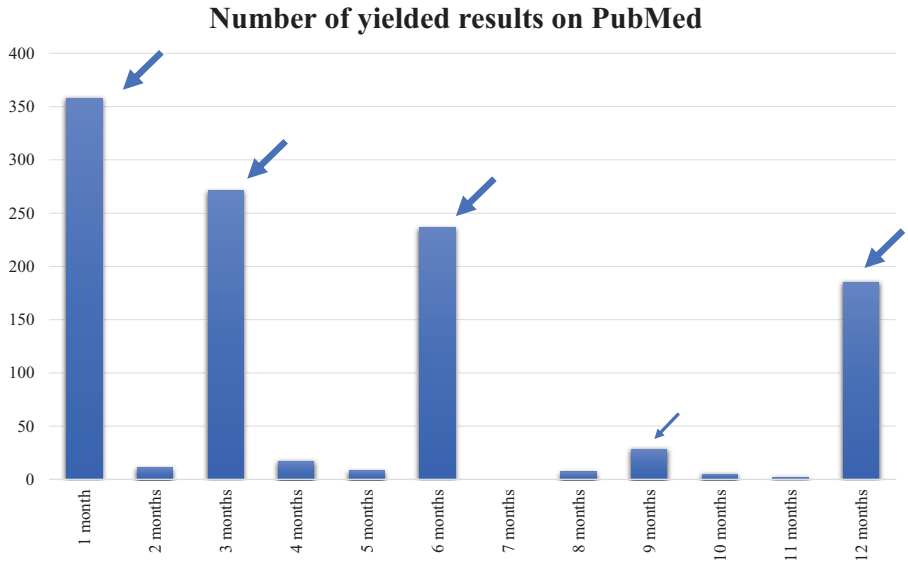

Figure 1. Number of yielded results on PudMed when typing 'x month' AND 'urology' with 'Clincal Trial' filter applied (while x is the number of months from 1 to 12).

This supremacy of the number 3 and its multiples is not founded in most cases on scientific evidence. When typing 'x month' AND 'urology' on PubMed with 'Clinical Trial' filter applied (while x is the number of months from 1 to 12), we noticed that the number of yielded results for each number of months confirms our hypothesis (Figure 1). Even when conducting well-developed clinical trials, follow-up of patients is done after 1 month (30 days), or 3, 6, 9 or 12 months, in 95.6% of trials. This could maybe facilitate fitting a schedule into a year for planning purposes.

Therefore, many of the presented clinical rules are time-related (hours, days, weeks, or months). This can remind us of the ancient Babylonian numbering system. Babylonians based their counts on the sexagesimal (also known as base 60 or sexagenary) which is a numeral system with 60 (12×5) as its base. This system has given its origins to the modern time units (e.g. 1 h $=$ 60 mins $=$ 60×60 secs). Babylonians also used the 'three' phalanges of each finger (except for the thumb) to count, making a total of twelve per hand. This might explain the origin of this 'temporal bias' unconsciously impacting our clinical opinion. Furthermore, the number three has a religious and cultural significance in many societies: the holy trinity in Christianity, the three daily prayers in Judaism, the triple Bodhi in Buddhism, etc. This concept has soaked to many life domains such as sports (triathlon), physics (the number of dimensions humans can perceive), and politics (the 'third'-world countries). We think that medicine in general, and not only urology, is also another life domain impressed by this 'number three' vestige.

To conclude, our common urological daily practice guidelines are possibly based on experts' opinions and seem logical for most healthcare practitioners. However, we think that they constitute leftovers of the 'inherited urology' from urology eminent ancestors, biased through the Babylonian origin of our time units, and cultural beliefs. Future well-developed evidence-based studies should target each step of our everyday urology practice.

Disclosure statement

All authors report no conflict of interest. All authors have read and approved the final version of the manuscript, and agree with the order of presentation of the authors.

Authors' contributions

Conceptualization: G. Mjaess and T Roumeguere; analysis: G. Mjaess, F. Aoun, S. Albisinni, M Vanhaeverbeek and T Roumeguere; writing – original draft: G. Mjaess; writing – review and editing: F. Aoun, S. Albisinni, M Vanhaeverbeek and T. Roumeguère; supervision: T. Roumeguere.

ORCID

Georges Mjaess http://orcid.org/0000-0002-8703-4611
Fouad Aoun http://orcid.org/0000-0002-8291-4302
Simone Albisinni http://orcid.org/0000-0001-5529-3064
Thierry Roumeguère http://orcid.org/0000-0002-5377-8137

References

[1] Sackett DL, Rosenberg WM, Gray JA, et al. Evidence based medicine: what it is and what it isn't. BMJ. 1996;312:71–72.
[2] Rizkallah M, Assi A, Otayek J, et al. What's important: foundations of orthopaedics-the "multiple-of-three rule": where is the evidence? J Bone Joint Surg Am. 2018;100:1165–1166.
[3] Funahashi Y, Yoshino Y, Sassa N, et al. Comparison of warm and cold ischemia on renal function after partial nephrectomy. Urology. 2014;84:1408–1413.
[4] Parekh DJ, Weinberg JM, Ercole B, et al. Tolerance of the human kidney to isolated controlled ischemia. J Am Soc Nephrol. 2013;24:506–517.
[5] Mellick LB, Sinex JE, Gibson RW, et al. A systematic review of testicle survival time after a torsion event. Pediatr Emerg Care. 2019;35:821–825.
[6] Desgrandchamps F, De La Taille A, Doublet JD, RetenFrance Study Group. The management of acute urinary retention in France: a cross-sectional survey in 2618 men with benign prostatic hyperplasia. BJU Int. 2006;97:727–733.

[7] Matsumoto K, Niwa N, Hattori S, et al. Establishment of the optimal follow-up schedule after radical prostatectomy. Urol Oncol Semin Orig Investig. 2018;36:341.e9–341-e14.
[8] Hori S, Tanaka N, Nakai Y, et al. Comparison of cancer detection rates by transrectal prostate biopsy for prostate cancer using two different nomograms based on patient's age and prostate volume. Res Rep Urol. 2019;11:61–68.
[9] Bolla M, de Reijke TM, Van Tienhoven G, et al.; EORTC Radiation Oncology Group and Genito-Urinary Tract Cancer Group. Duration of androgen suppression in the treatment of prostate cancer. N Engl J Med. 2009;360:2516–2527.
[10] Nabid A, Carrier N, Martin A-G, et al. Duration of androgen deprivation therapy in high-risk prostate cancer: a randomized phase III trial. Eur Urol. 2018;74:432–441.

Georges Mjaess
Urology Department, University Clinics of Brussels, Hôpital Erasme, Université Libre de Bruxelles, Brussels, Belgium
Hôtel Dieu de France, Université Saint Joseph, Beyrouth, Liban

Fouad Aoun
Hôtel Dieu de France, Université Saint Joseph, Beyrouth, Liban
Urology Department, Institut Jules Bordet, Université Libre de Bruxelles, Brussels, Belgium

Simone Albisinni
Urology Department, University Clinics of Brussels, Hôpital Erasme, Université Libre de Bruxelles, Brussels, Belgium

Michel Vanhaeverbeek
Laboratory of Experimental Medicine, ULB 222, Université Libre de Bruxelles, CHU Charleroi, Charleroi, Belgium

Thierry Roumeguère
Urology Department, University Clinics of Brussels, Hôpital Erasme, Université Libre de Bruxelles, Brussels, Belgium
Urology Department, Institut Jules Bordet, Université Libre de Bruxelles, Brussels, Belgium
Laboratory of Experimental Medicine, ULB 222, Université Libre de Bruxelles, CHU Charleroi, Charleroi, Belgium
thierry.roumeguere@erasme.ulb.ac.be

Received 20 April 2020; revised 3 June 2020; accepted 28 June 2020