Intravesical treatment of painful bladder syndrome: the potential pitfalls of meta-analyses

Sanjay Sinha

Received: 4 March 2012 / Accepted: 4 March 2012 / Published online: 9 May 2012
© The International Urogynecological Association 2012

Intravesical therapy is an important component in the therapeutic options for managing painful bladder syndrome-interstitial cystitis (PBS-IC). The literature is sparse with very few good quality, adequately powered studies. Matsuoka et al. [1] have made a valiant attempt to make sense of the literature regarding intravesical therapy for PBS-IC. This paper could, unfortunately, become a case study in the flaws of using meta-analysis.

The key finding of this paper is the recommendation for using intravesical BCG (bacillus Calmette–Guerin) for the treatment of PBS-IC. This is based on a meta-analysis of two double-blind randomized controlled trials, the multicenter North American study [2] and the study by Irani et al. [3]. The larger, and more rigorous (265 patients), National Institutes of Health (NIH)-sponsored, North American trial did not show any benefit with intravesical BCG against the placebo, intravesical saline. There was a low response rate and the difference between the two arms was not statistically significant. Subsequently, non-responders were offered open label BCG, again with a low 18 % response rate [4]. Conversely, responders from this trial were followed for an additional 34 weeks to assess for durability of response [5], which was similar in patients who responded to placebo compared with BCG. The investigators concluded that BCG was not effective for the treatment of PBS-IC.

The study by Irani [3] of 30 patients randomized to intravesical BCG and intravesical saline showed a high (73 %) response rate that was durable. However, patient populations were not well-defined with inadequate details regarding entry

criteria and prior or concomitant treatments. Alternate patients were given therapy and placebo. Details about the BCG used are not provided and the flow of patients from screening to follow-up has not been stated. Follow-up is exceptionally good without any apparent loss of data despite approximately 360 data collection points. In the historical context of the response of PBS-IC to various treatments, the response rate is exceptionally high and durable. Equally astonishing is the lack of any adverse events in either group, despite ample literature evidence of a significant complication rate with intravesical BCG [6].

One of the important criticisms of meta-analyses has been the dilution of good quality studies by poorer quality ones, as statistical methodology does not differentiate the quality of work. As long as there are a reasonably large number of studies analyzed and the heterogeneity is low, this problem is minimized. However, when one performs meta-analysis with a very small number of studies (as is the case here, just two studies regarding BCG have been combined), there is a very real risk that an unreasonable conclusion might result, more so if the two studies differ in their conclusions [7]. Use of meta-analysis also ignores the importance of the two open label extension groups of the North American trial that further reinforced the conclusions of the main study. Combining the multi-centered North American trial with the single-center report of the much smaller numbers from Irani et al. has "tipped the balance of statistical significance" for the combined numbers.

The reason for the differing conclusions of these two studies can only be speculated upon. Treatment allocation in the study by Irani et al. was based on alternation rather than true randomization. The Consort statement 2010 [8] recommends against using this method of treatment allocation in view of the difficulty in concealing allocation leading to selection bias and its consequences. Lack of adequate

S. Sinha (✉)
Department of Urology, Apollo Hospital,
Hyderguda,
Hyderabad 500029, India
e-mail: drsanjaysinha@hotmail.com

details regarding entry criteria in the study by Irani et al. make it impossible to compare the patient groups. Such inadequacy of entry criteria in reports of trials is not uncommon [9] and may render the trial unusable for others. The small sample size of the study by Irani is another crucial factor. The pitfall of using small samples in trials for PBS-IC has been discussed previously [10]. The authors have acknowledged the marked heterogeneity of these two trials. Perhaps a better method of collecting evidence on this subject might have been a systematic review without resorting to meta-analysis.

The best method of securing evidence in medicine remains a well-performed large randomized trial [11], and such a trial is already available in the form of the NIH-sponsored study. The conclusions of this trial have been strong enough for various guidelines to recommend against the usage of BCG in the treatment of PBS-IC. The recently released American Urological Association (AUA) guidelines [12] have suggested six lines of treatment with stepwise escalation. BCG does not figure in this exhaustive list, but instead is mentioned in the list of treatments that should not be offered. The European Urology guidelines do not even mention BCG in their list of possible treatments [13].

In this regard it is instructive to read the latest edition of *Campbell's Urology* [14]. The author has summarized the various intravesical therapies in tabular form, along with the level of evidence and grade of recommendation. The level of evidence for all the therapies that are commonly in use is less than level one, with the exception of hyaluronic acid, which has level one evidence, but comes with a grade D recommendation. BCG and resiniferatoxin come with level one evidence and a grade A recommendation *against* their use!

As mentioned, Matsuoka et al. [1] have made a valiant attempt. However, I believe their study could leave readers with a misleading conclusion, one that is at variance with all major established treatment guidelines, despite being based on essentially the same studies.

The article is a sobering reminder of the paucity of quality clinical research in PBS-IC.

References

1. Matsuoka PK, Haddad JM, Pacetta AM, Baracat EC (2012) Intravesical treatment of painful bladder syndrome: a systematic review and meta-analysis. *Int Urogynecol J*. doi:10.1007/s00192-012-1686-2
2. Mayer R, Propert KJ, Peters KM et al (2005) A randomized controlled trial of intravesical bacillus calmette-guerin for treatment refractory interstitial cystitis. *J Urol* 173:1186–1191
3. Irani D, Heidari M, Khezri AA (2004) The efficacy and safety of intravesical Bacillus-Calmette-Guerin in the treatment of female patients with interstitial cystitis: a double-blinded prospective placebo controlled study. *Urol J* 1:90–93
4. Propert KJ, Mayer R, Nickel JC et al (2007) Did patients with interstitial cystitis who failed to respond to initial treatment with bacillus Calmette-Guerin or placebo in a randomized clinical trial benefit from a second course of open label bacillus Calmette-Guerin? *J Urol* 178:886–890
5. Propert KJ, Mayer R, Nickel JC et al (2008) Follow-up of patients with interstitial cystitis responsive to treatment with intravesical bacillus Calmette-Guerin or placebo. *J Urol* 179:552–555
6. Hall MC, Chang SS, Dalbagni G et al (2007) Guidelines for the management of non muscle invasive bladder cancer (stages Ta, T1, and Tis). *J Urol* 178:2314–2330
7. Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions*. Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org
8. Moher D, Hopewell S, Schulz KF et al (2010) CONSORT 2010 Explanation and Elaboration: updated guidelines for reporting parallel group randomised trials. *J Clin Epidemiol* 63:1–37
9. Hall JC, Mills B, Nguyen H, Hall JL (1996) Methodologic standards in surgical trials. *Surgery* 119:466–472
10. Propert KJ, Payne C, Kusek JW, Nyberg LM (2002) Pitfalls in the design of clinical trials for interstitial cystitis. *Urology* 60:742–748
11. LeLorier J, Grégoire G, Benhaddad A, Lapierre J, Derderian F (1997) Discrepancies between meta-analyses and subsequent large randomized, controlled trials. *N Engl J Med* 337:536–542
12. Hanno PM, Burks DA, Clemens JQ et al (2011) AUA guideline for the diagnosis and treatment of interstitial cystitis/bladder pain syndrome. *J Urol* 185:2162–2170
13. Fall M, Baranowski AP, Elneil S et al (2010) European Association of Urology guidelines on chronic pelvic pain. *Eur Urol* 57:35–48
14. Hanno PM (2011) Bladder pain syndrome (interstitial cystitis) and related disorders. In: Wein AJ, Kavoussi LR, Novick AC, Partin AW, Peters CA (eds) *Campbell's urology*, 10th edn. Elsevier, Philadelphia, pp 357–401