

Comment on U S Seth, et al. (J Pak Med Assoc. 73: 69 -73, 2022)

## Effect of preoperative intravenous steroids on seroma formation after modified radical mastectomy

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Madam, I read with interest the article by Seth et al.<sup>1</sup> entitled 'Effect of preoperative intravenous steroids on seroma formation after modified radical mastectomy' published in the January 2023 issue of JPMA.<sup>1</sup> The authors report their single centre randomised experience of administering a single preoperative dose of injected methylprednisolone acetate, which was observed to decrease postoperative seroma formation- seen from a reduced mean volume of fluid drained and mean duration of drainage between women who received a modified radical mastectomy with steroids, relative to those who received a modified radical mastectomy alone, for breast cancer.<sup>1</sup>

Whilst the conclusions seem valid, it may not be appropriate to label this work as a 'case-control' study based on the authors' description of their methodology, given that patients were randomised.<sup>1</sup> Case-controlled studies (CCS) have a different design and answer a different question than cohort studies and randomised controlled trials (RCT), which is what this paper appears to be.<sup>2</sup>

In CSS, researchers use cases that have an outcome of interest- an outcome that has already developed. Researchers then select controls and match the cases to the controls who are similar in important baseline/demographic and clinically relevant characteristics except for the outcome of interest being absent in controls. The investigators then look back temporally to investigate the presence of exposure in the cases that may be absent in controls. Thus case-controlled studies are, by definition, retrospective in nature and crucially investigate evidence/association of exposure, not outcome.<sup>2</sup> The odd's ratio (which is used in this paper) is used to quantify the difference between the presence of the exposure of interest in the cases compared to controls, but more importantly, odds ratios should not be used to quantify difference in outcome of interest between the groups.<sup>3</sup>

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The methodology the authors employed is that of an RCT. RCTs are prospective in nature, yet the methods section states this to be a 'case-control study was conducted from November 2020 to April 2021. After approval of the institutional ethics review board, the sample size was calculated.' As with any RCT, the investigators enrol a group of people at risk of developing an outcome of interest. In this case, that is seroma formation following modified radical mastectomy surgery. An intervention is evaluated in the experimental arm, which in this case is injectable methylprednisolone acetate. The outcome of the experimental arm can then be compared to the control arm (those who did not receive steroids). When the outcome of interest develops in both groups, investigators may use relative risk to quantify the difference between the incidence of outcome observed in the cohort with the intervention being evaluated (experimental arm) and the group that did not receive the intervention of interest (the control arm) which is what was done in this study.<sup>3</sup> Perhaps one of the most famous example of a CCS is by Wynder and Graham<sup>4</sup>, which established the association between cigarette smoking and lung cancer.<sup>5</sup> The investigators collected information on exposure status from cases with the outcome of interest (lung cancer), matched these to appropriate controls and retrospectively evaluated the presence of the exposure under investigation (cigarette smoking). In this instance, it was appropriate to use an odds ratio as the quantification was the odds of finding the exposure in those who had already developed the outcome. This is important to distinguish from relative risk, which quantifies the risk (relative) of developing the outcome of interest in those who have the exposure/intervention being investigated. The temporal sequence is thus flipped. CCS, thus, provide weak evidence of association.

Given that this was a prospective RCT, a relative risk should be employed. Odds ratios should not be used to quantify differences in the outcome because odds ratios tend to generate larger differences between exposed and non-exposed; this may lead to spurious associations, and an overestimate of the effect size.<sup>3</sup> This is especially true when the outcome of interest is not rare- as is the case

here.<sup>3</sup> Other appropriate quantifiers may include the incidence rate ratio, which is useful if there is a longer follow-up time in one group over the other.

We must be correct in labelling the study methodology as this has fundamental implications for the type of analysis that should be employed. CCS are also an inferior form of evidence compared to RCTs, so I am not sure why the authors assert their methodology to be a CCS, whereas their study is clearly prospective and has randomised allocation to treatment. Could this be to do with the type of analysis used? If this was an RCT, why did the authors not register the trial on an appropriate registry, as is expected practice?

It is also very important to acknowledge sources of bias. Biases are systematic methodological errors that may encourage one outcome over another.<sup>5</sup> Performance bias and detection bias are two important biases not acknowledged in the limitations section at the end of the discussion. Performance bias is systemic differences between groups in the care provided or exposures to care other than the intervention of interest (consciously or subconsciously).<sup>5</sup> Detection bias is when systematic differences exist between groups in determining outcomes.<sup>5</sup> A simple solution to both of these sources of bias which should have been incorporated, given their relative ease and simplicity, are placebo and blinding. Blinding participants to the intervention being received and blinding the surgical team/outcome assessors to the

intervention being administered would have significantly strengthened the results obtained, as biases affect the accuracy of results.<sup>5</sup>

Despite the problems with the analysis and reporting, I still believe this paper has internal validity and probably external validity (although all participants were Pakistani). I congratulate the author for their efforts but wanted to use this as an opportunity to highlight the importance of recognising appropriate study design, conducting the correct statistical analysis, and proper acknowledgement of the limitations of one's work and ways in which its' limitations may be improved upon.

## References

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