French Editorial from the ACHBPT

A Japanese multi-institutional randomized controlled trial (ND-Trial)

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Comment on: Arita J, Sakamaki K, Saiura A, *et al.* Drain Placement After Uncomplicated Hepatic Resection Increases Severe Postoperative Complication Rate: A Japanese Multi-institutional Randomized Controlled Trial (ND-trial). Ann Surg 2021;273:224-31.

Submitted Feb 01, 2021. Accepted for publication Feb 25, 2021.
doi: 10.21037/hbsn-21-57
View this article at: http://dx.doi.org/10.21037/hbsn-21-57

We read with great interest the recently (*Annals of Surgery*, Feb, 2021) published article by Arita and collaborators (1) about the clinical impact of a no-drain policy in liver resections. The aforementioned study (ND-trial) is the first multi-institutional randomized controlled trial (RCT) assessing the impact of a drain placement after liver resection on the severe postoperative complication rate.

The use of drains in liver surgery has been established since decades. It is based on the assumption that it will permit monitoring of bleeding or biliary leak as well as mitigating the consequences of such an event. However, advances in the perioperative management of liver resection have led to significantly low bleeding complications (<1%) (2). On the other hand, authors using routine drainage recommend early drain removal (before postoperative day 3) in order to reduce the incidence of retrograde bacterial infections despite the fact that most biliary leakages appear on or after the 5th–7th postoperative day (3,4). The role of drain insertion is thus under ongoing debate.

Previous performed RCTs, most of which already date more than 10 years (5-9), did not support routine drainage following uncomplicated liver resection. However, the conclusions from these studies should be attenuated due to the limited sample size, the low methodological quality and the high heterogeneity in the definition of severe complications. Furthermore, most of these studies were conducted before introduction of the widely accepted Clavien-Dindo classification (10,11).

Based on the results of the present RCT study, the authors suggest that drains should not be placed after hepatic resections in patients who do not exhibit a high risk of postoperative bile leakage or bleeding. Indeed, their results underlined that severe complications (C-D score ≥3) as well as bile leakage were significantly lower in the no-drain group, while wound-related complications were comparable in the two groups. Interestingly, subgroup analysis did not identify any high-risk group for which drain placement could prove beneficial.

Despite the high quality of this study, we would like to raise several comments. First, the authors proceeded to patient randomization once liver resection had been completed. Thirty-seven patients considered to be of high risk for bile leakage because of a rough and complex liver transection surface were thus excluded although initially enrolled in the study. Unfortunately, selection of low-risk patients could introduce major selection bias and results should be interpreted with caution. Moreover, it would have been important to state the criteria on which patients were classified as high or low risk for bile leakage. Indeed, only a small number of patients presented risk factors of bile leakage such as increased BMI, blood loss, hypoalbuminemia, increased indocyanine green clearance rate at 15 min, long operative time or repeated liver resections, while other common risk factors such as blood transfusion were not taken into account (12).

Previous studies have shown that major or central liver resections and non-anatomical resections are more frequently associated with biliary leakage (from 12% to

30%) when compared with minor resections (from 4.5% to 8%) (2,13-15). Since laparoscopic liver resections seem to have an acceptably low rate of biliary leakage (2.8–6.2%), no series suggested any specific benefit on this specific complication (14). In the present study, laparoscopic and open surgery approaches were comparable between the two groups but we should keep in mind that minor hepatectomies represented the majority of liver resections (87% and 85% in the drain and no-drain group, respectively). This low percentage of major 'high-risk' hepatectomies is also revealed by the relative low bile leak rate of 8% in the drain group. Relative patient selection was finally reflected by a low rate of severe complications (5%), which is lower than the one reported in the literature (8–13%) (5,6). Last but not least, several other exclusion criteria such as the second step of a 2-stage hepatectomy or "other conditions considered to be inappropriate for inclusion in the study" could have been clarified in the Discussion section.

The authors initially chose a non-inferiority setting for outcome analysis, which was secondarily switched to a superiority analysis. Per protocol (PP) analysis is generally accepted for non-inferiority trials but an intent-to-treat population (ITT) analysis could have been a reasonable choice, given past literature on no-drain policies, as it tends to avoid the over-optimistic estimates of efficacy that result from PP analysis.

In conclusion, this study is the first RCT study to enroll a large number of patients based on a statistical design in order to assess the impact of a no-drain policy on the severe postoperative complication rate. As is so often the case, robust conclusions that favor one particular treatment cannot be drawn for all types of liver resection. However, a no-drain policy for patients having a low risk of postoperative bile leak or bleeding appears to be superior in terms of postoperative severe complication rates.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office of *Hepatobiliary Surgery and Nutrition*. The article did not undergo external peer review.

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-21-57/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Tzedakis S, Fuks D. A Japanese multi-institutional randomized controlled trial (ND-Trial). HepatoBiliary Surg Nutr 2021;10(2):226-228. doi: 10.21037/hbsn-21-57

