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PROSPER Trial For Rectal Prolapse: A Study Meant To Stay In The Annals Of History

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I. Introduction

The PROSPER trial, a randomized study conducted by Senapati et al.,[1] aimed to compare different surgical treatments for rectal prolapse. This ambitious study is commendable for its scale and scope, being the largest randomized trial in this specific area of colorectal surgery. The PROSPER trial, comparing rectopexy and resection rectopexy, was the largest study with 270 patients, resulting in a severe underpowered study. The Birmingham-based study, strongly publicized and endorsed by ACPGBI, was published in all major journals. The trial showed no differences between various sub groups, such as abdominal or perineal procedures, Suture and mesh rectopexy and Delerome's and Atemteier's procedures. The study's sub-optimal sample size and power analysis should not be hyped, as it could lead to blind belief in the results. It is crucial to consider what is important for patients and what is not, to avoid making patients test models. The trial presents several limitations and challenges that warrant critical discussion.

II. Study Design And Methodology

The study employs a pragmatic, factorial (2x2) design, allowing randomization between abdominal and perineal surgeries and between different techniques within these categories. This design is commendable for its flexibility and potential to address multiple questions within a single trial framework. However, the decision to allow surgeons to choose whether to participate in one or both randomizations introduces a level of selection bias. This could potentially skew the results, as surgeons' preferences and experiences might influence the outcomes.

Moreover, the use of a computerised minimised randomisation procedure aimed to ensure balanced groups for variables such as age, incontinence levels, and physiological status. While this approach is sophisticated, it might not fully account for all potential confounding factors. The trial's robustness would have benefited from a more detailed stratification process to ensure a comprehensive balance between the groups.

Strengths of the Study

1. **Large Sample Size**: The PROSPER trial is notable for its large sample size compared to previous studies on rectal prolapse. The trial only recruited 293 patients out of its original target of more than 950 with only 270 getting actually surgery, so it may not be appropriate to consider the results as evidence of equivalence between the abdominal and perineal approaches. With 213 patients randomized (perineal procedures), it surpasses other studies, such as those comparing suture rectopexy with resection rectopexy (78 patients), which included only 49 patients between abdominal vs perineal.
2. **Comprehensive Comparisons**: The study's inclusion of multiple surgical techniques (suture rectopexy, resection rectopexy, Delorme's, and Altemeier's procedures) provides a broad comparison, offering valuable insights into the efficacy and outcomes of different approaches
3. **Quality of Life Assessment**: Unlike previous trials, PROSPER evaluated the quality-of-life post-surgery, demonstrating significant improvements in patients' symptom-specific and overall quality of life across all surgical procedures

Weaknesses and Limitations

1. **Recruitment Challenges**: One of the significant limitations of the PROSPER trial was the difficulty in recruitment. Difficulty of recruitment was not only at the level of patients but also at the level of surgeons. Despite extensive advertisement and efforts to publicise it at the ACPGBI meeting. The ACPGBI efforts brought the initial interest from 82 UK centres, but only 30 centres managed to randomize patients. This under-recruitment hugely impacted the study's power and the ability to detect more nuanced differences

between surgical techniques. More than 950 patients in total and at least 280 in each arm would have shown some statistical difference. They recruited 293 patients and 213 were randomised with 48 patients in each group. Difficulty at the patient level was seen in counselling. It was a difficult task in consultation and consenting the patients due to surgical equipoise.

2. **Inadequate Power for Certain Comparisons**: The trial's design aimed to compare abdominal and perineal procedures; however, only 49 patients were randomized in this comparison. Again, more than 950 patients in total were targeted but 293 recruited and only 270 managed to get some sort of surgery and follow up. At least 280 in each arm would have shown some statistical difference, but we had figures like, 23 vs 26, 38 vs 40 and 106 vs107. These figures are nowhere near the original target figure some are one tenth of the figure. This low number limits the statistical power to detect significant differences, particularly in recurrence rates, which are a primary concern for surgeons. The results are "no statistically significant difference".
3. **Participant Recruitment and Randomization:** The recruitment of 293 patients is a significant achievement, but the distribution of participants among the randomization groups reveals disparities. For example, only 49 patients were randomized between the surgical approaches, compared to 78 for abdominal procedures and 213 for perineal procedures. This uneven distribution raises concerns about the statistical power of some comparisons, particularly those involving fewer participants. The higher recurrence rates observed, although not statistically significant, could be a consequence of these disparities and the resulting lack of power.
4. **Demographic Discrepancies**: The study included patients from different geographical regions, such as Europe and India, with significant demographic differences. For instance, the patients randomized in India were younger and predominantly male, differing from the older, primarily female population in Europe. These demographic variances could affect the generalisability of the findings. There were some changes of protocols in the middle of trial.
5. **Variability in Surgical Expertise**: The trial acknowledged that some surgeons were unfamiliar with certain procedures, particularly Altemeier's operation. Although training was provided, some surgeons could not perform alternative procedures and some continued with their preferred practice. Some participants changed their preference for a particular procedure and stayed with one of their proffered one. Some had problems with lack of protected time for research. Some surgeons resisted to change of personal practice. There can be significant variations in surgical techniques among surgeons, which may have influenced the results of the trial. Standardization of surgical procedures could improve the comparability of outcomes in future studies.
6. **Higher-Than-Expected Recurrence Rates:** The trial's results showed higher recurrence rates than expected, but no significant differences between the treatments. However, some studies suggest that recurrence rates may be higher after perineal repairs than abdominal repairs, but randomised controlled trials have not confirmed this. Factors like age at surgery and follow-up duration may also be predictors of recurrence. The trial observed recurrence rates of rectal prolapse that were higher than anticipated, regardless of the surgical approach. This raises questions about the long-term effectiveness of the procedures studied. Despite the higher recurrence rates, the trial failed to demonstrate significant differences in outcomes between the various surgical techniques compared. This makes it challenging to definitively recommend one approach over another.
7. **Limited Sample Size:** While the PROSPER trial was relatively large compared to previous studies, it may still have been underpowered to detect significant differences between treatment groups, especially for certain outcomes.
8. **Focus on Short-Term Outcomes:** The trial primarily focused on outcomes up to 3 years post-surgery. Longer-term data is essential to assess the durability of the surgical interventions and potential late complications.
9. **Limited Assessment of Quality of Life:** The trial found that all procedures significantly improved quality of life from baseline. However, some say that quality of life has been poorly reported and investigated in this patient population. While the trial did assess quality of life, the depth of this assessment could be enhanced in future studies to provide a more comprehensive understanding of the impact of different treatments on patients' overall well-being.
10. **Outcome Measures:** The primary outcome measures focused on the recurrence of prolapse, incontinence, bowel function, and quality of life (QoL) scores. The use of well-validated tools such as the Vaizey incontinence score and EQ-5D for QoL is a strength of the study. However, the follow-up period of up to three years, while adequate, might not capture the long-term recurrence rates and QoL changes fully. Rectal prolapse is a condition with potentially long-term outcomes, and a longer follow-up could provide more definitive insights.
11. **Results and Interpretation:** The trial's results indicated no significant differences in recurrence rates, bowel function, or QoL between any of the surgical treatments compared. While this finding suggests that all procedures are similarly effective, the high recurrence rates observed across all groups (e.g., 24% for

Altemeier's vs. 31% for Delorme's) are concerning. These rates are higher than those reported in previous studies, prompting questions about the trial's external validity and the surgical expertise of the participating centers.

12. **Surgical Expertise and Training:** The trial included a mentoring system and video training for surgeons, particularly for the less familiar Altemeier's procedure. While this is a positive step towards standardizing the surgical techniques, the effectiveness of this training is not fully clear. The potentially varied skill levels among surgeons could have influenced the outcomes, particularly the high recurrence rates. Future studies should consider more stringent criteria for surgical expertise and possibly centralizing surgeries to a few high-volume centres.

III. Discussion

Surgical treatments for rectal prolapse are scarce, and the PROSPER trial makes an important contribution to the small amount of knowledge on these treatments. However, when doing future research, it is important to overcome the difficulties associated with recruiting by utilising more rigorous procedures to guarantee acceptable sample sizes across all comparisons. In addition, the reliability and usefulness of the findings could be improved by using a patient population that is more like previous studies.

Changes were made to the trial's protocol while the researcher was conducting the study. Although it is not unusual for clinical trials to have difficulties throughout their execution, such as problems relating to the recruitment of participants or the practicality of the study, these difficulties have the potential to result in adjustments to the protocol.

Problems with the feasibility of the study: If a certain treatment arm is proving to be difficult to recruit patients for, or if surgeons are reluctant to undertake a particular technique, then changes might be considered. **Issues about safety**: In the event that one of the treatment groups has unanticipated adverse effects, the protocol may be altered in order to address safety issues.

Emerging evidence: it is possible that new study findings will require modifications to the protocol in order to integrate the most recent information.

The fact that any modifications to the protocol of a clinical research are normally subject to a thorough examination and approval by an **ethical committee** is something that should be taken into consideration. This is done to ensure that the study is both **safe and honest.**

Furthermore, boosting the training and **standardisation of surgical** methods among the surgeons who participated in the study should help reduce the variability in results that is caused by disparities in competence. Finally, **extended follow-up** periods may provide a more accurate picture of the rates of recurrence and the quality of life that patients experience after surgery over the long term [3-5].

Taking a look at the statistical analysis of the PROSPER trial, it is possible that the determination of the sample size was made more difficult by a number of issues in the instance of the PROSPER study.

There were probably many outcomes that were evaluated during the experiment, and each of these outcomes required its own individual estimate of the sample size.

Statistical analysis that is difficult to understand: the process of analysing several treatment groups and comparing them to a control group might make the computations more difficult to understand.

Unknown effect size: It is possible that the actual difference between the treatments was not known in advance, which makes it challenging to precisely estimate the sample size that is required.

Importance of Conducting Power Analysis

A power analysis is often carried out by researchers in order to accomplish the task of determining the ideal sample size for a clinical trial. Taking into account the anticipated magnitude of the effect as well as other aspects, this statistical technique assists in estimating the number of participants that are required to reach the necessary level of power. In the PROSPER experiment, there were more than 950 patients in total, and there were at least 280 patients in each arm. This required a statistically significant difference to be observed. A total of 293 patients were recruited, only 270 got surgery 213 (perineal procedures) were randomly assigned to participate in the study ie Altemeier's vs Delorme's procedure (106 vs 107), making it the largest study ever conducted to compare, suture rectopexy with resection rectopexy (38 Vs 40) and abdominal vs Perineal (23 vs 26) which comprised a total of only 48 patients.

We were required to have 280 patients in each arm and a total of more than 950 people; however, we are currently only dealing with some 40 patients and a total of 270 patients (not even touching one arm alone). An underpowered study, sometimes referred to as a severe or substantially underpowered study, is what this is. Since the study was based in Birmingham and was multicentric, received extensive publicity, and was supported by ACPGBI, we have not ruled out the possibility of publication bias. The study was published in all the main publications.

Imagine you are going to consent a patient for an abdominal or perineal procedure, and you are going to take into consideration consenting a patient who is healthy and who has read about this study on the internet. Since the patient is aware that there is no distinction between an abdominal or perineal operation, a robotic/lap or open procedure, Altemeier's or Delorme's procedure, the patient is willing to go with the technique that is the complete opposite of what you believe to be the best option for him or her. what you intend to do, and how you intend to persuade the patient. It is expected that you will provide further references; however, the patient will return to the PROSPER trial.

We are of the opinion that such studies, which have a sample size or power analysis that is not up to opinion, should not receive such a great deal of attention that everyone, including members of the medical community, begin to blindly believe about them. Due to the fact that the majority of us glance at the journal and consider its impact factor to be a guarantee of trust and honesty. All of the things that are publicised are not the set standards, and all of the things that are not published in high impact journals are not completely sub-standard. By keeping a sifter in our minds, we need to be able to distinguish between what is significant for applying to our patients and what is not; otherwise, our patients will be put through the same process as test subjects.

IV. Conclusion

However, even though the PROSPER trial represents a significant advancement in the field of colorectal surgery research, the results of the trial must be viewed considering the constraints that were placed on it. For enhancing the management of rectal prolapse and building on the insights gained from this study, it is vital to conduct additional research with populations that are larger and more diverse, as well as to standardise surgical training. On top of that, the surgical treatment for external rectal prolapse had undergone certain modifications. When compared to 1997, the number of surgeons who preferred a robotic/laparoscopic abdominal approach increased enormously in 2024, while the number of surgeons who used perineal techniques fell.[6,7] The PROSPER trial need to continue to be an essential component of our surgical history, and its significance ought to be confined to the archives of the past. The study's substandard sample size and power analysis should not be hyped, as it could lead to blind belief in the results. It is crucial to consider what is important for patients and what is not, to avoid making patients test models.

Conflict of Interest: None

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