Pediatric Research, Risk, and Paravertebral Blocks

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Visoiu et al.1 compared the pain management benefits of paravertebral nerve blocks (PVBs) versus laparoscopic cholecystectomy. One study arm received 6 ropivacaine injections into the paravertebral space and 4 normal saline injections at the laparoscopic port sites, and the other arm received 6 normal saline injections at the laparoscopic port sites, and the other arm received 6 normal saline injections at the paravertebral space and 4 ropivacaine injections at the laparoscopic port sites. The use of sham PVBs in pediatric patients in this population illustrates some of the complexities of pediatric ethics.

Research in pediatric patients starts with the Federal Policy for the Protection of Human Subjects, U.S. Department of Health and Human Services, 45 CFR 46 Subpart D, Additional Protection for Children Involved as Subjects in Research.2 Each of the 4 ascending categories of pediatric research requires greater scrutiny of the risk-to-benefit ratio (Table 1).

If we were asked to assess this study, we might classify it as “Research involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject’s disorder or condition…which is of vital importance” (Table 1, No. 3). This classification permits exposing the child to a “minor increase over minimal risk,” which is to how the classification is colloquially referred. Here, we will focus on minimal risk, minor increase over minimal risk, the concept of direct benefit, and the implications of sham procedures.

MINIMAL RISK AND MINOR INCREASE OVER MINIMAL RISK

There are questions about what constitutes minimal risk, much less minor increase over minimal risk. The Presidential Commission for the Study of Bioethical Issues, the Secretary’s Advisory Committee on Human Research Protections, and the Institute of Medicine endorse the “absolute” concept of minimal risk, which is the risk to which healthy children living in safe environments are exposed.

The “reasonable parent standard,” another interpretation of minimal risk, proposes accepting risks that would be approved by a reasonable parent, such as snowboarding, swimming, and playing contact sports. This approach has been criticized because it is unclear as to what risks would be acceptable to a reasonable parent and because children benefit by participating in these higher-risk activities of childhood.

Rid et al.3 proposed a mechanism for assessing the risks of clinical research. The process is to identify harms, define the magnitude of harms, quantify the likelihood of harms occurring, and compare the likelihood of the harm occurring to a comparative harm.

To assess for minimal risk, we can use the risk of pneumothorax in PVB, which has been suggested to be 0.5% per adult patient receiving a multiple-injection PVB.4 Although not all pneumothoraces require intervention, we propose that this would be classified as a moderate magnitude of harm comparable to a broken leg, in that the event may cause discomfort and require treatment. A small magnitude of harm, described by a common cold or a headache, does not seem to rise to the level of pneumothorax; a significant magnitude

Table 1. Federal Classifications for Pediatric Research

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<th>1. Research not involving greater than minimal risk.</th>
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<td>a. IRB determines minimal risk.</td>
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<td>b. IRB finds and documents that adequate provisions are made for soliciting assent from children and permission from their parents or guardians.</td>
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<th>2. Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects.</th>
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<td>a. IRB justifies the risk by the anticipated benefit to the subjects.</td>
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<td>b. The relation of the anticipated benefit to the risk is at least as favorable as that presented by available alternative approaches.</td>
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<th>3. Research involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the disorder or condition of the subject.</th>
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<td>a. IRB determines the risk represents a minor increase over minimal risk.</td>
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<td>b. The intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations.</td>
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<tr>
<td>c. The intervention or procedure is likely to yield generalizable knowledge … which is of vital importance for the understanding or amelioration of disorder or condition of the subject.</td>
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<tr>
<td>d. Adequate provisions for assent and permission.</td>
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<th>4. Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children.</th>
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of harm, described by requiring surgery and rehabilitation, seems too severe. For children older than 6 years of age, the risk of a broken bone while playing basketball is 180 per million instances or 0.018%. In this case, the risk of a pneumothorax is greater than the risk of a broken bone, suggesting that this risk is at least a minor increase over minimal risk.

A minor increase over minimal risk is characterized by pain, discomfort, and stress that are transient, reversible, and not serious. IRBs may also consider the experience of the physician performing the intervention in making this determination.

The minor increase over minimal risk classification requires the knowledge to be of “vital importance.” If the risk of PVBs warrants a study to assess for the adequacy of an alternate technique, and the risks are not that well defined, it is difficult to determine whether insertion of PVBs can be considered a minor increase above minimal risk. If the risks of the PVBs are low, this research is less important. If the risks of PVBs are higher, making this study of vital importance, then it becomes difficult to consider PVBs to be a minor increase over minimal risk.

Whether adult data should be used to assess risk depends in part on the population and the likelihood that risks and outcomes will differ between pediatric and adult populations. For example, because this study population had an average age of 14 years and an average mass of 64 kg, it seems reasonable to use adult risk data.

But that brings up a sticky point. If adult risk data are applicable, then adult outcome data are likely applicable. If there are no adult outcome data, it may be more appropriate to do the research in adults rather than in children when it is unclear whether the risks abut or exceed a minor increase over minimal risk.

DIRECT BENEFIT TO THE PATIENT

We classify this study as having no direct benefit to the patient because those not participating in the study can choose whether they want PVBs, laparoscopic site injections, or both PVBs and laparoscopic site injections. That is, this is neither a matter of making something available only through participation in research nor a matter of decreased risk in 1 study arm because both study arms received needle entry into the paravertebral space. This does not mean that the study is unnecessary; determining whether PVBs improve pain management is important. But it does mean that there is no direct benefit to being in the study.

It has been proposed that the psychological benefits from participating in research provide a direct benefit. This argument can be abused, and it is unclear when the potential psychological benefits of participation are sufficient to outweigh the risks in this study. Although it has been argued that adolescents older than 14 years can take greater risks because they have more developed decision-making capability, it is unclear as to what extent of risk they can authorize.

SHAM PROCEDURES

Performing research using sham procedures requires exquisite attention to determining the need for the sham procedure, minimizing risk within the context of good research practices, and ensuring that the results of the study will be valuable and worth the risks taken.

The authors “felt that the lack of an invasive placebo would invalidate the study findings,” so they did sham PVBs with normal saline injections. Researchers may want to consider whether this level of invasiveness significantly improves the study. For example, if researchers are concerned that fluid in the paravertebral space may affect results, then sham PVBs are necessary. However, if that is not a concern, researchers should consider whether less invasive interventions suffice, such as a skin nick or a needle entry to a level deeper than the skin, but not into the paravertebral space.

PERFORMING AND ASSESSING PVB PLACEMENT

One concern about this study is the absence of confirmation of a successful block. In 2010, using studies through May 2008, it was reported that the rate of partial or failed PVBs in adults was between 0% and 13%. It is understandable that the researchers did not use postoperative analysis of sensation because that would affect the ability to perform a blinded study, but the use of nerve stimulation may have provided some information about appropriate placement.

Of course, if this study was undertaken now, ultrasound would likely be used to confirm correct placement. But this brings up a point for future researchers to consider. We will use this study to set the stage, but we are not suggesting that this consideration was relevant at the time.

Imagine that while designing the protocol, researchers recognize that ultrasound likely would be the favored technique for PVB placement in the near future. Researchers then may want to consider postponing the study until it could be done with ultrasound. Postponing could avoid the problem of having a technological advance render the study approach less desirable. For example, if doing a loss-of-resistance technique was standard when the study was designed, but ultrasound became the preferred technique midway through the study, the researchers are in the uncomfortable position of using the less desirable technique in the latter part of the study.

PEDiatric RESEARCH AND FEDERAL REGULATIONS

This editorial is not designed to criticize the authors or the study. It is designed to point out the complexities of pediatric research and the usefulness of the federal regulations. There is legitimate concern that the strict requirements surrounding pediatric research limit beneficial research. But there is a tension between protecting subjects and advancing the science. Regulations provide framework and guidance to help IRBs and researchers navigate through this tension.

DISCLOSURES

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