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Injured versus *Uninjured Afferents*

Who Is to Blame for Neuropathic Pain?

THE role of different classes of afferents in neuropathic pain is a controversial issue. The debate revolves around two questions: (1) What is the role of injured and uninjured afferents in neuropathic pain? (2) What is the role of myelinated and unmyelinated fibers? Although it is commonly accepted that sensitization of central pain-processing neurons is involved in neuropathic pain, it is unclear what afferents induce and maintain central sensitization under neuropathic conditions. A better understanding of the changes in injured and uninjured afferents after nerve injury is needed to improve strategies for the treatment of chronic pain. In this issue of ANESTHESIOLOGY, Sapunar *et al.*[1] describe the electrophysiologic properties of isolated neurons from the L4 and L5 dorsal root ganglia after an L5 spinal nerve injury in rats. An advantage of the L5 spinal nerve ligation (SNL) model[2] is that injured and uninjured neurons reside in different dorsal root ganglia, but their axons commingle in the sciatic nerve and target tissue (fig. 1). Like other animal models of neuropathic pain, SNL results in behavioral signs of spontaneous and stimulus evoked pain (*i.e.*, mechanical and thermal hyperalgesia).

What is the evidence that injured afferents are to blame for neuropathic pain? An obvious clinical example comes from patients with a traumatic nerve lesion that resulted in the development of a neuroma: Touching or tapping the neuroma produces paraesthesia and pain. Injection of local anesthetics at the site of the nerve injury may relieve not only ongoing pain but also mechanical hyperalgesia in the surrounding skin.[3] Neuroma resection and relocation of the proximal nerve end may also produce pain relief in these patients. In animal neuroma models, ectopic mechanical sensitivity, thermosensitivity, and chemosensitivity as well as spontaneous activity are found in injured myelinated *and* unmyelinated afferents,[4] and this is thought to be the neuronal basis of pain generated from neuromas in humans.

Similar to other lesions of peripheral nerves, SNL results in neuroma formation. After SNL, however, development of spontaneous activity in injured afferents is restricted to myelinated nerve fibers, because it seems to be absent in injured unmyelinated afferents.[5] The article by Sapunar *et al.* provides additional evidence that myelinated (but not unmyelinated) injured (but not uninjured) neurons develop enhanced excitability. Input from injured afferents seems to be important for the neuropathic pain behavior because application of tetrodotoxin to the L5 dorsal root ganglion reduces signs of mechanical hyperalgesia after SNL[6] and because application of neomycin or gadolinium to the proximal, cut end of the L5 spinal nerve immediately after injury prevents or diminishes signs of mechanical hyperalgesia.[7] Signs of mechanical hyperalgesia develop within hours after the lesion, similar to development of spontaneous activity in injured myelinated afferents, suggesting a causal link between the two.[5] Studies that have used dorsal rhizotomies in the SNL model to directly investigate the role of injured afferents in neuropathic pain have unfortunately led to contradictory results: Some found reversal of neuropathic pain behavior,[8] whereas others reported that an L5 dorsal rhizotomy did not prevent or reverse mechanical hyperalgesia.[9] The interpretation of these data are complicated by the finding that dorsal rhizotomy by itself can produce signs of neuropathic pain.[10]

Is there a role for injured, *unmyelinated* afferents in neuropathic pain? Evidence for a role comes from the observation that artemin reversed the behavioral signs of neuropathic pain[11] and normalized the SNL-induced changes in small L5 DRG neurons as well (*e.g.*, IB4 binding; expression of P2X3, CGRP, galanin, and NPY). Artemin is a member of the glial-derived neurotrophic factor family, and the accessory protein GFRα3, through which it signals, is predominantly expressed in unmyelinated, nociceptive primary afferent neurons.[12]

The presence of mechanical hyperalgesia after an L5 ganglionectomy[13] or an L5 ventral rhizotomy[13,14] is direct evidence for a role of *uninjured* afferents in neuropathic pain. Both manipulations exclude injured primary afferents as contributors to neuropathic pain because either the soma of the injured neuron is removed (ganglionectomy) or only motor efferents are injured (ventral rhizotomy). Furthermore, there is accumulating indirect evidence for a role of uninjured afferents in neuropathic pain. The following evidence was mainly but not exclusively obtained in the SNL model. Uninjured afferents develop adrenergic sensitivity[15,16] and an increased sensitivity to tumor necrosis factor α.[17] Uninjured afferents also up-regulate neuropeptides,[18,19] neurotrophic factors,[20,21] and signal transduction proteins (*e.g.*, TRPV1).[22] After L5 spinal nerve injury, the percentage of

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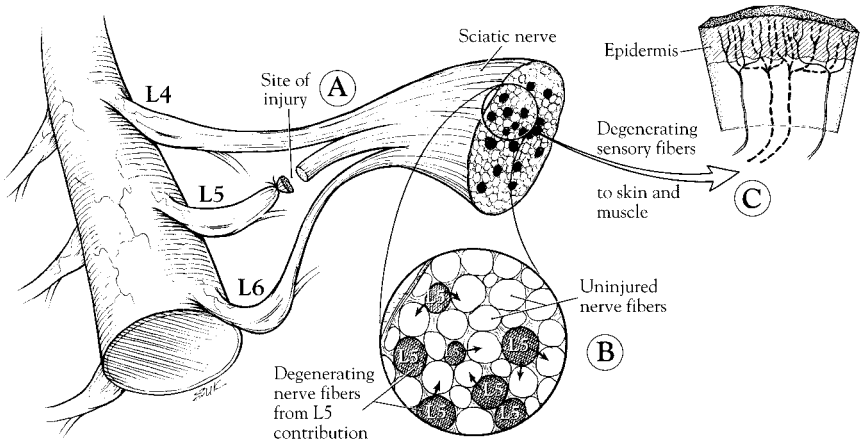

Fig. 1. Schematic drawing of the L5 spinal nerve ligation. (*A*) In the L5 spinal nerve ligation, the ventral ramus of the L5 spinal nerve is ligated and cut proximal to the lumbar plexus. (*B*). In the sciatic nerve, degenerating large and small L5 nerve fibers are in close proximity to uninjured nerve fibers from other spinal levels (including L4). Factors released during Wallerian degeneration of the injured fibers may affect function in uninjured nerve fibers (*arrows*). (*C*) Commingling of injured and uninjured nerve fibers also occurs in peripheral target tissues such as skin. Artwork provided by Ian Suk.

cold-sensitive neurons in the L4 DRG is increased,[23] and the responsiveness of uninjured, unmyelinated L4 afferents to natural stimuli is augmented.[24] $Na_V1.8$, a tetrodotoxin-resistant sodium channel, is redistributed into the peripheral axons of uninjured afferents after spinal nerve injury.[25] Antisense oligonucleotides directed against $Na_V1.8$ reverse neuropathic pain in the SNL model.[25] Morphologic studies furthermore suggest that uninjured, unmyelinated afferents sprout into the "injured" L5 spinal cord segment.[26] *In vivo* recordings from the L4 dorsal root, L4 spinal nerve, or peripheral primary afferents have shown that uninjured myelinated and unmyelinated nerve fibers develop spontaneous activity after spinal nerve injury.[16,27,28] Spontaneous activity in uninjured, unmyelinated nociceptive afferents was present in rats within 24 h after SNL. Although the rate of discharge was low, approximately half of the unmyelinated fibers showed spontaneous activity; therefore, this low rate of discharge could be sufficient to induce central sensitization. Microneurographic recordings from unmyelinated fibers in patients with neuropathic pain reveal that mechanically insensitive afferents become spontaneously active and responsive to mechanical stimuli.[29]

The mechanisms inducing changes in uninjured afferents are not understood. Because intact axons commingle with degenerating axons, factors associated with Wallerian degeneration may be involved. Neuropathic pain behavior is reduced in situations where Wallerian degeneration is delayed or diminished.[30,31] Wallerian degeneration leads to the generation of multiple factors, some of which are classic inflammatory mediators known to excite or to sensitize nociceptive afferents. Some of these mediators are released within hours after peripheral nerve lesion[32] and therefore could induce the early changes seen in uninjured L4 afferents after L5 SNL.

Changes in uninjured afferents may also occur and contribute to neuropathic pain accompanying infectious (*e.g.*, human immunodeficiency virus, herpes zoster) and metabolic (*e.g.*, diabetes) diseases or in neuropathy due to drug treatment (*e.g.*, vincristine). In neuropathic pain, several etiologies may be at work simultaneously: the primary disease (*e.g.*, trauma, diabetes) and secondary events (*e.g.*, Wallerian degeneration). The relative importance of these factors to the development and maintenance of neuropathic pain remains to be resolved.

Matthias Ringkamp, M.D., * **Richard A. Meyer, M.S.** * Johns Hopkins University, Baltimore, Maryland. platelet@jhmi.edu

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Does Botulinum Toxin Have a Role in the Management of Myofascial Pain?

BOTULINUM toxin type A (BoNT-A) was approved by the U.S. Food and Drug Administration in 1989 for the treatment of strabismus and blepharospasm. It was subsequently approved for cervical dystonia and, most recently, for hyperhydrosis. It provides effective symptomatic relief of these conditions for several months, and repeated treatments usually provide similar benefits when symptoms recur. It has been reported to be effective for a variety of off-label indications, including other dystonias, myoclonus, spasticity associated with stroke, head injury, multiple sclerosis and cerebral palsy, sialorrhea, and smooth muscle hyperactivity.[1] For the past several years, there has been increasing interest in the use of BoNT-A for the treatment of pain. Myofascial pain syndrome would seem to be a logical condition to study, because it has been proposed that motor hyperactivity is involved in the development and possibly maintenance of this painful condition. Previously published open-label studies have shown mainly positive results. This is not surprising given the fact that saline injection and dry needling of trigger points are accepted therapeutic interventions. Placebo-controlled studies have yielded conflicting results. In this issue of ANESTHESIOLOGY, Ferrante *et al.*[2] report the results of a randomized, double-blind, placebo-controlled trial of BoNT-A for the treatment of cervical and shoulder myofascial pain. It is a robust study involving 132 patients, saline placebo and three different BoNT doses, and a 12-week follow-up period. All previous medications were stopped before the study, and identical postinjection therapy was given to all patients. There were no significant differences in pain scores, pressure algometry, or analgesic use among the control and three BoNT groups.

The negative results of this study are unexpected because there is reason to predict reduction of pain given the pharmacologic effects attributed to BoNT. Reduction in muscle tone and activity is a predictable result of intramuscular injection, and it would seem reasonable to postulate that a period of prolonged muscle inactivity would be of benefit for a condition characterized by muscle shortening and tenderness. In addition, there is evidence that BoNT interferes with the release of substance P, calcitonin gene–related protein (CGRP), and other neurotransmitters or neuromodulators found in nociceptors.[3] The so-called SNARE protein, which is necessary for exocytosis of acetylcholine vesicles and is inhibited by BoNT, is also present in substance P and CGRP-containing neurons.[4]

As the authors indicate, the site of trigger point injection may not be the optimal site for BoNT injection of the muscle. The motor endplate is the most effective location for injection, but that site is not known for many of the muscles susceptible to myofascial pain.

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Nevertheless, BoNT diffuses throughout the muscle and should provide some effect at the higher doses.

Another concern is the accuracy of the diagnosis and the possible heterogeneity of the cohort selected. Not all patients who have muscle tenderness have myofascial pain syndrome. Also, patients who have myofascial pain that is secondary to other painful disorders such as radiculopathy, facet arthropathy or complex regional pain syndrome are much more resistant to treatment than patients with primary myofascial pain syndrome. It might be useful to limit study participation to patients who experience complete but temporary relief from local anesthetic trigger point injections.

The effect of BoNT on several other painful disorders has been investigated. Foster *et al.*[5] conducted a double-blind, placebo-controlled trial of BoNT for the treatment of low back pain. At both 4 and 8 weeks, the treatment group had significantly more patients reporting pain relief, and at 8 weeks, functional improvement was greater in the treatment group. I was able to find five placebo-controlled trials of BoNT injection for chronic tension type headache published between 1999 and 2004. Only one of these studies indicated a significantly better response for BoNT. There have been a few case reports on the use of BoNT in neuropathic pain states, including complex regional pain syndrome and spinal cord injury, but no controlled trials. The fact that preganglionic sympathetic neurons are cholinergic has led to speculation that prolonged sympathetic denervation by BoNT may be feasible.

Although BoNT has been shown to block the release of substance P, CGRP, and glutamate *in vitro*, there has been little evidence that BoNT produces clinically relevant reduction in release of neurotransmitters or neuromodulators in nociceptors. Two studies have failed to demonstrate changes in cutaneous pain thresholds in human volunteers after subcutaneous BoNT infiltration.[6,7] It is possible that the dose requirements for these effects are not met using clinically appropriate doses.

Compared with the dramatic benefits seen for patients with dystonia, spasticity, and hyperhydrosis, the outcomes for treatment of patients with chronic pain have been mixed at best. This is typical for new therapies for chronic pain, because most cohorts of patients with a given diagnosis contain individuals with diverse pain mechanisms and psychosocial backgrounds. We often find individual patients within a group who respond dramatically while the group as a whole does not have significant improvement. Refinement of indications, injection technique, and dose may eventually better define criteria for successful treatment of certain pain syndromes using botulinum toxin.

Stephen E. Abram, M.D., Medical College of Wisconsin, Milwaukee, Wisconsin. sabram@mcw.edu

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Deciding Whether Your Hospital Can Apply Clinical Trial Results of Strategies to Increase Productivity by Reducing Anesthesia and Turnover Times

THIS issue of ANESTHESIOLOGY includes three articles describing the use of overlapping anesthesia induction to perform more cases in a regular workday.[1–3] The purpose of my article is to assist readers in deciding whether the studied interventions would increase productivity (work completed per $ cost) in their operating rooms (ORs).

The three articles used induction rooms slightly differently. The details are of large practical importance, because simply stating that induction rooms were used does not capture the issues of staffing and patient flow. Nevertheless, I leave such details to readers, because they are straightforward. If the recipe is followed, likely most any facility will achieve the same reported reductions in nonoperative times. In contrast, whether such reductions in anesthesia-controlled and turnover times will result in an increase in productivity varies markedly among practice settings. Results are highly sensitive to how OR time is allocated and cases are scheduled.

While considering the examples,

- Hospital A: Fixed hours of OR time, add-on cases not used to fill ORs
- Hospital B: Fixed hours of OR time, add-on cases used to fill ORs
- Hospital C: Surgeon open access to OR time, more than 8 h of cases a day
- Outpatient A: Surgeon open access to OR time, less than 8 h of cases a day
- Outpatient B: Fixed hours of OR time,

you may consider your situation to be a combination of examples. If so, I will have succeeded at showing why quantitative methods to consider the balances automatically[4] are important tools for OR and anesthesia group management.

This Editorial View accompanies the following three articles: Hanss R, Buttgereit B, Tonner PH, Bein B, Schleppers A, Steinfath M, Scholz J, Bauer M: Overlapping induction of anesthesia: An analysis of benefits and costs. ANESTHESIOLOGY 2005; 103:391–400; Torkki PM, Marjamaa RA, Torkki MI, Kallio PE, Kirvelä OA: Use of anesthesia induction rooms can increase the number of urgent orthopedic cases completed within 7 hours. ANESTHESIOLOGY 2005; 103:401–5; Sandberg WS, Daily B, Egan M, Stahl JE, Goldman JM, Wiklund RA, Rattner D: Deliberate perioperative systems design improves operating room throughput. ANESTHESIOLOGY 2005; 103:406–18.

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Hospital A: Fixed Hours of OR Time, Add-on Cases Not Used to Fill ORs

A surgeon sees patients and operates on them in the next available opening. Patients wait on average 3.5 weeks for surgery. Occasionally, from the random ebb and flow of patients and/or the surgeon's vacation, the surgeon's queue extends to 6 weeks.

The surgeon has allocated OR time Mondays from 7:00 AM to 3:00 PM. The OR finishes at

- 10th percentile 1:00 PM
- 25th percentile 1:15 PM
- 50th percentile 1:50 PM
- 66th percentile 2:00 PM
- 80th percentile 2:20 PM
- 90th percentile 3:00 PM.

The surgeon has few short cases that can fill the remaining OR time at the end of the day in the OR. Also, whether the last case would be performed would be unpredictable, because on the day of surgery, if a case would not be expected to finish by 3:00 PM, the case is cancelled, resulting in patient inconvenience and frustration. The managers focus on preventing overutilized OR time.

United States readers should appreciate that, at Hospital A, OR time is not being allocated (*i.e.*, staffing is not being adjusted) based on OR workload. The surgeon is thankful for the 8 h of OR time budgeted to him or her by the hospital, not *vice versa*. On a long-term (*e.g.*, 1 yr) basis, more OR time may be budgeted, but that is irrelevant to the issue at hand.

Hanss *et al.*[1] showed that for Hospital A, the use of overlapping induction can reduce anesthesia-controlled and turnover times sufficiently for an extra, brief (< 1.5 h) case of another surgeon to be performed each day. This applies provided patients are admitted or are otherwise available to have surgery *only* if there is a sufficient reduction in time that day for the case.[1]

Hospital B: Fixed Hours of OR Time, Add-on Cases Used to Fill ORs

Hospital B matches A, except that managers try to fill remaining OR time with cases. Managers keep lists of potential add-on cases, both inpatients and outpatients

available to be contacted the day before surgery. As many hours of these add-on cases as possible are scheduled.[5,6] An extrashort case can fit at the end of the day in each of several ORs.[5,7] Thus, remaining, unscheduled add-on cases are relatively long (*i.e.*, > 2 h).

At Hospital B, the use of overlapping induction may not result in a sufficient reduction in anesthesia controlled and turover times to be able to perform additional cases.[7] Hospital A matches that described by Hanss *et al.*[1] in that their underutilized OR time averaged 1.9 h per OR per day. Because their newly scheduled cases had OR times of less than 1.5 h,[1] some of those cases could have been scheduled without the use of overlapping induction.

Anesthesia providers at Hospital A should focus first at converting OR scheduling to that of Hospital B and then make efforts to initiate overlapping anesthesia induction. This applies particularly to anesthesia providers who work at but are not employed by Hospital A. Sandberg *et al.*[3] showed that the successful use of overlapping induction to increase productivity results in a benefit to patients and surgeons, with no overall change in hospital plus anesthesia net margin. Yet, overlapping induction increased anesthesia providers' costs by 21%, with no increase in revenues.[3] In contrast, changing case scheduling causes no increase in costs, and an increase[5] in revenue for hospital and anesthesia providers.

Hospital C: Surgeon Open Access to OR Time, More Than 8 h of Cases a Day

A surgeon sees patients in the clinic on Tuesdays and performs surgery on them typically 6 days later. Depending on the need for medical evaluations, insurance approval, and so forth, surgery is sometimes 13 days later.

The surgeon's cases enter the OR at 7:00 AM. Finish times are

- 10th percentile 1:00 PM
- 25th percentile 2:00 PM
- 50th percentile 3:00 PM
- 66th percentile 5:00 PM
- 80th percentile 6:00 PM
- 90th percentile 7:00 PM.

The OR workload varies a lot, depending on the random arrival of patients' requests for surgery. The surgeon sometimes has two cases and sometimes has four.

At Hospital C, managers allocate OR time on a short-term basis (*i.e.*, adjust staffing) based on OR efficiency, to provide the surgeon with the right amount of OR time, neither too much nor too little.[4,8] Managers consider the ratio of the cost of 1 h of overutilized OR time to 1 allocated hour to be 2:1. Thus, one third of allocated ORs should finish late, and two thirds should finish early. Staffing for the 66th percentile (*i.e.*, two thirds) provides the surgeon with an allocation Mondays from 7:00 AM to 5:00 PM.[9] For days when the surgeon finishes after 5 PM, staff sign up months in advance to work late if needed, being paid overtime (OR nurses) and bonuses (anesthesiologists).

The use of overlapping induction is unlikely to increase the number of cases performed during allocated (scheduled) hours at Hospital C, because there are no additional cases to be performed.

I designed the scenario to show that overlapping induction can still increase productivity by reducing the costs to perform the existing cases. The OR workload could be reduced sufficiently for the surgeon to be allocated 8 h instead of 10 h for the same cases.[4,8]

The return on investment in implementing overlapping induction depends on the proportion of ORs for which OR allocation could be reduced. Cost reduction is achievable when there are many services allocated, at baseline, more than 10 h of OR time on a workday.[8] Frequently there are not.[4,8] Also, managers need to judge whether allocated OR time would be reduced or remain the same because of organizational (political) resistance to change.

The impact of reducing turnover and anesthesia-controlled times on costs depends on the differences between actual and scheduled OR times,[10,11] variability among days in the surgeons' workload,[4,8] absolute workload,[4,8] and the number of turnover times to be reduced.[3,11] The result can be determined by analyzing a facility's OR and anesthesia information system data. I have not determined a way to guess answers, because findings differ among surgeons, groups, and departments at the same facility.[3,8] Generally, the more the variability is, the less the benefit is, whereas the more the workload and the turnovers are, the larger the benefit is. If a surgeon, group, or specialty completely fills (> 8 h) an OR every Tuesday with many short cases, large reductions in turnovers and anesthesia-controlled times can result in increased productivity. For example, consider Surgeons 1 and 2 in the article by Sandberg *et al.*[3] Surgeon 1's workload was reduced from 8.9 h to 8.5 h and averaged one turnover per day. In contrast, Surgeon 2's workload started at 9.9 h and was reduced more, to 8.7 h, because the surgeon averaged four turnovers per day. To understand why day-to-day variability in workload matters, suppose that on half of the workdays, Surgeon 2 had averaged 4 h of cases, and on the other half did 15.8 h of cases in two ORs each staffed for 10 h. Then, there would be no cost benefit to reducing turnover and anesthesia-controlled times.

The scenario at Hospital C applies to hospitals for their medically urgent cases. The cases must be performed. Of course, in that setting, reducing turnover and anesthesia-controlled time can result in an additional case being performed during the regular workday (*e.g.*, 7 AM to 3 PM), provided the reduction in time is large enough and the additional case is short enough.[2] The question whose an-

swer will vary among hospitals is whether such a reduction in turnover and anesthesia-controlled time results in a net increase or reduction in costs (*i.e.*, increases productivity).

I have not mentioned the issue of the surgeon who often schedules to work slightly more than 8 h but chooses on his or her own not to work longer hours. In other words, the bottleneck is not the day-to-day variability in workload or the hospital and anesthesia providers, but the surgeons' desire to work late. These circumstances differ from those of previous studies that my colleagues and I have performed showing the relative lack of impact of reducing turnover and anesthesia-controlled times on performing an additional case(s).[4,11] Unlike in our previous studies, OR time is not fixed, meaning that if a case is scheduled, it is performed even if it would run late on any one day. This is why the findings of Surgeons 3 and 4 in Sandberg *et al.*[3] and the urgent cases in Torkki *et al.*[2] were expected. Surely, reducing turnover and anesthesia-controlled times can result in performing additional cases during the workday. Neither article showed an increase in productivity (work completed per $ cost) in this setting, only the potential for it to occur.

Outpatient A: Surgeon Open Access to OR Time, Less Than 8 h of Cases a Day

A surgeon operates at Outpatient A every Friday from 7:00 AM until

- 10th percentile 1:00 PM
- 25th percentile 1:30 PM
- 50th percentile 1:55 PM
- 66th percentile 2:10 PM
- 80th percentile 2:30 PM
- 90th percentile 3:00 PM.

Managers consider this adjusted utilization of 86% to be good, because many surgeons' allocated OR times are less than 60%.

Like Hospital C, at Outpatient A, the surgeon limits OR workload, not availability of OR time. If the surgeon brought more cases to the facility, staffing would be adjusted to fit the workload. Because often that would mean finishing after 3:00 PM, managers may encourage the surgeon to operate on another day. However, that is irrelevant to the issue at hand. The premise of OR allocation would be to match staffing to the surgeon's workload, not *vice versa*.

If there were a direct effect of the use of overlapping anesthesia induction on productivity at Outpatient A, it would be by reducing labor costs. However, reducing turnover and anesthesia-controlled times cannot result in reduced overutilized OR time in this scenario, because there is no overutilized OR time.[4,8] Allocated hours cannot be reduced, because the surgeon will still have the staffed OR for the day. Labor costs and anesthesia staffing are a fixed cost of the number of staffed ORs (*i.e.*, the first case of the day starts).

Outpatient B: Fixed Hours of OR Time

Gynecologists share allocated OR time at Outpatient B on Fridays. They do many brief cases. They have an adjusted utilization of 92%. They have a patient queue of 7 weeks. The limits on their incomes are not their personal work hours, but the lack of OR time.

The use of overlapping induction may increase the number of patients treated by the gynecologists, but it may not. The key issue is whether there are sufficient outpatients who would be satisfied to be told that they can have their surgery in fewer days if they were to receive care within one of a few consecutive afternoons. A fundamental feature of the intervention of Hanss *et al.*[1] was to have patients available who would have surgery on an *ad hoc* basis. If patients must be scheduled reliably, reducing the anesthesia-controlled and turnover times may not result in completion of additional cases.[11] Because of large mean absolute differences between scheduled and actual case durations for surgery, large reductions in time are needed to schedule an extra case into an OR *reliably*.[11]

Readers would miss an important point if they look at the clinical trial of Hanss *et al.*[1] as just one of overlapping induction of anesthesia. At facilities for which lack of OR time limits patient care, do everything you can to resist or change the paradigm that patients have to know within a few days of surgery when they will have surgery. The availability of a pool of patients who are flexible, in exchange for receiving prompt care, may be fruitful.

Conclusions

The three articles in this issue of ANESTHESIOLOGY study different situations. Hanss *et al.*[1] consider fixed hours of OR time, with cases performed only when the OR time was reduced. Torkki *et al.*[2] studied medically urgent orthopedic trauma patients, wherein all cases were performed, the issue being the time of the day when done. Sandberg *et al.*[3]studied increases in cases when limited by the surgeons or longer-term institutional culture. Provocatively, none of these scenarios overlap with the conditions studied by previous investigations of the impact on productivity of reducing turnover and anesthesia-controlled times.[4,7,11]

Franklin Dexter, M.D., Ph.D., The University of Iowa, Iowa City, Iowa. franklin-dexter@uiowa.edu

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