How robot assistance and innovative local pain treatment can be a strong combination to enhance recovery after minimal invasive spine surgery (MISS)

J.G. Steverink, MD, J.J. Verlaan, MD PhD*, H.R. Jonkman, MD*, F.R. van Tol, MD*, B.J. Oosterman, PhD*, A.R. Vaccaro, MD PhD§.*

** SentryX B.V., Austerlitz, Netherlands. § Rothman Orthopedic Institute, Philadelphia, PA, United States.*

Introduction

To improve outcomes after surgery, reduce postoperative hospital stay and increase the efficiency of health care, a shift towards optimization of all facets of the perioperative process is taking place in spine surgery. The philosophy of improving outcome by optimization of the perioperative process is embodied by the Enhanced Recovery After Surgery (ERAS) society. Two major pillars of the ERAS philosophy are minimizing the impact of surgery and tailoring pain treatment to individual patient needs. This paper discusses important developments in these two ERAS pillars for spine surgery, and their potential synergy: first the utility of robot assistance during surgery and, second, the added value of an innovative local pain treatment that is being developed to relieve pain after surgery.

(Robotic) MISS

Minimally invasive spine surgery (MISS) has steadily gained popularity over the past years, due to limiting the extent of tissue damage, decreasing blood loss and allowing shorter hospital stay compared with open surgery.[1–4] However, the patient and surgical team are exposed to significantly more radiation as MISS relies heavily on intra-operative fluoroscopy.[5]

Providing a further refinement of MISS, the use of robotic systems in spine surgery is a novel and exciting development in the field.[6] The portion of spinal interventions performed with robotic systems is currently small but expected to increase considerably in the near future. Various robotic spine surgery systems are commercially available, such as the ROSA Spine system (Zimmer Biomet Robotics, Montpellier, France), the ExcelsiusGPS system (Globus Medical, Audubon, PA, USA) the TiRobot orthopedic robot system (TINAVI Medical Technologies, Beijing, China) and the Mazor X system, which was preceded by the SpineAssist and Renaissance system (Medtronic, Dublin, Ireland). Notwithstanding the high initial costs and steep learning curve[7], robotic systems could lead to more efficient allocation of healthcare personnel by automation of routine processes. Although the superiority of robotic pedicle screw implantation *versus* unassisted implantation has not unequivocally been demonstrated, its potential advantages include[7–9]:

i) increased accuracy of pedicle screw placement by guiding the implantation trajectory,
ii) Less variation in operative time as a result of a more detailed preoperative planning,
iii) decreased radiation exposure, as routine diagnostic preoperative imaging (CT) voids the need for fluoroscopy.

Especially when robotics and minimally invasive spine surgery are combined, these advantages can further enable enhanced recovery after surgery. By reducing tissue dissection, variation in surgery time, radiation exposure and risk of pedicle screw misplacement, as little harm as possible is done to the patient.[4,7,8]

Sustained non-opioid pain relief after surgery

Spine surgery ranks amongst the most painful interventions overall, inhibiting rapid recovery after surgery and thus extending the length of stay in the hospital. While (robotic) MISS limits the extent of soft tissue dissection, the densely innervated vertebral bone and specifically the periosteum are still damaged by instrumentation, contributing significantly to

postoperative pain.[4,10–13] Multi-modal opioid-sparing pain treatment is strongly recommended by the ERAS society, but opioids are still required to keep the pain after MISS at an acceptable level.[3,8,14–16] Opioid-Related Adverse Drug Events (ORADEs) such as nausea, drowsiness, reduced gastro-intestinal mobility and respiratory depression occur in the majority of patients consuming opioids after orthopedic surgery, and are a major contributor to extended hospital stay.[17,18] ERAS further recommends employing intra-operative local anesthetic techniques.[15] Examples of these techniques include local infiltration analgesia and regional blocks. In spine surgery specifically, liposome bupivacaine local infiltration or erector spinae plane (ESP)-blocks can be applied.[19,20] Increasing literature shows opioid- and pain-reducing effects of both liposome bupivacaine and ESP blocks, but these effects are mostly limited to a 24-hour postoperative window.[19–21] Liposome bupivacaine is infiltrated into both sides of the surgical wound at the subcutaneous and deeper muscle level. In ESP blocks, bupivacaine or ropivacaine solution is administered in the fascial plane of the erector spinae muscle at the lateral tip of the transverse process. The presumed mechanism of action is an interfascial spread of local anesthetic solution toward the posterior branches (rami) of spinal nerves. Through interfascial spread, multiple spinal levels can be anesthetized by a single administration. The success of both methods depends on correct administration (Figure 1).

As severe pain after spine surgery typically lasts three days, the duration of analgesia provided by ESP blocks or liposome bupivacaine is insufficient.[22,23] In addition, both ESP blocks and liposome bupivacaine administration can be cumbersome, time-consuming and require training of the operator to achieve expertise in administration. For example, the recommended administration method for liposome bupivacaine in spine surgery requires up to 40 injections, and ESP blocks require ultrasound/fluoroscopy guidance towards the target site. ESP blocks are administered pre-operatively, after which the anatomy of the ESP block location is perturbed by surgical dissection and accurate placement of local anesthetic agents could be compromised.

An operator-independent and durable opioid-free analgesic for use in spine surgery is an unmet clinical need. To this end, SentryX develops BR-003, an implantable sustained-release formulation of bupivacaine for use in instrumented spine surgery.[24] BR-003 is co-implanted with pedicle screws and provides over 72 hours of bupivacaine release. The entry point of pedicle screws into the vertebra and thus the location of BR-003 closely resembles the target location of ESP blocks (Figure 1 and 2). In contrast to the preoperatively administered ESP-block, no further surgical dissection takes place at the administration site after BR-003 implantation. Preclinical studies show that the resulting local bupivacaine levels remain well above neurophysiological active thresholds for 72 hours following BR-003 implantation.[25,26] Following drug release, BR-003 is gradually resorbed by the body. Key features of BR-003 are:

i) Simple administration by co-implantation with pedicle screws (Figure 1 and 2),
ii) Proven effective location to decrease pain after spine surgery,
iii) A minimum of 72 hours of high local bupivacaine concentrations, matching the duration of severe postoperative pain.

Pain and ORADEs impede recovery after surgery.[3,16,17] By providing accurate and localized non-opioid pain relief that potentially reduces the need for systemic opioid-based therapy and risk of downstream adverse effects, as little harm as possible is done to the patient. BR-003 is compatible with virtually all polyaxial pedicle screw systems, and all commonly used surgical approaches. In contrast to ESP blocks, BR-003 is co-implanted with each pedicle screw and thus inherently scales with the number of vertebral levels involved in the procedure.

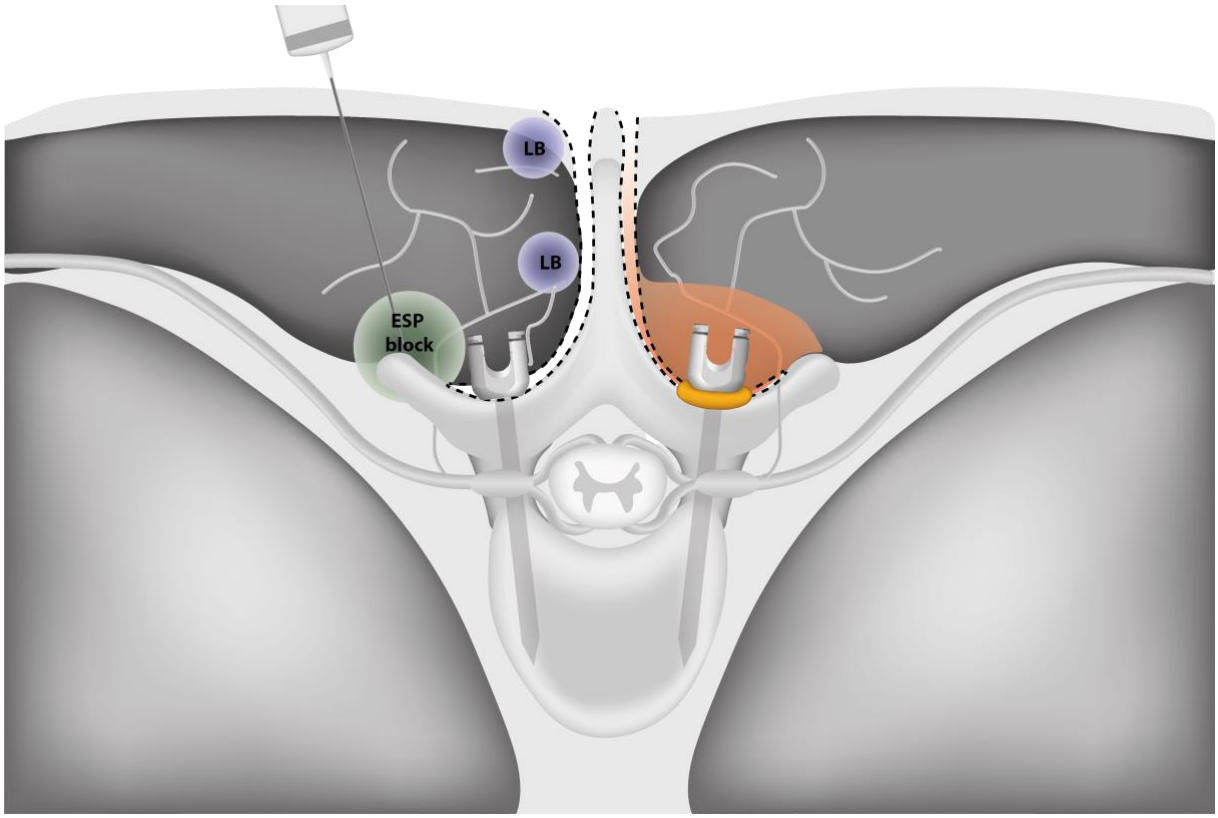

Figure 1 *Axial view of trunk and placement of local anesthetic when employing liposome bupivacaine (LB, purple), ESP block (green) and BR-003 (orange) in open spine surgery. The area of spread of local anesthetic from BR-003 matches the ESP block and liposome bupivacaine, while its accurate placement does not depend on expert administration.*

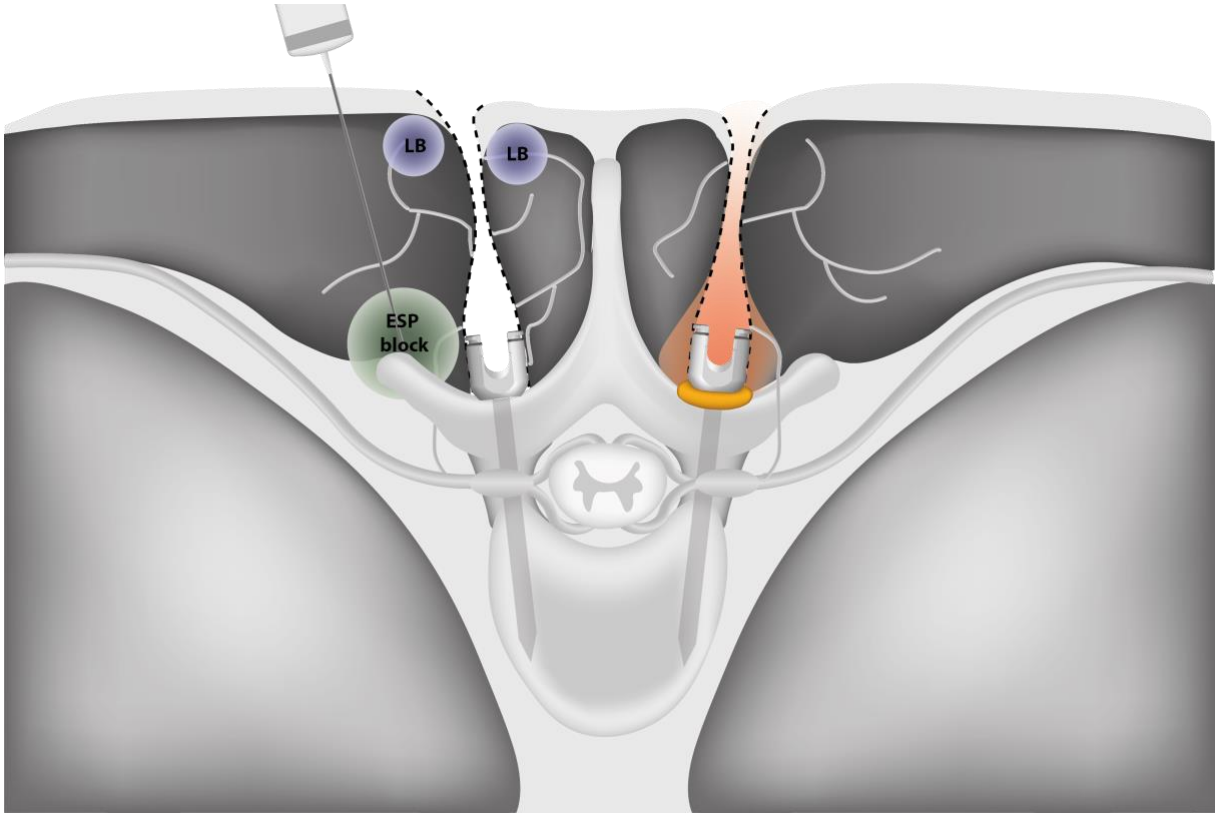

Figure 2 *Axial view of trunk and placement of local anesthetic when employing liposome bupivacaine (LB, purple), ESP block (green) and BR-003 (orange) in minimally invasive spine surgery (MISS).*

Anticipated advantages of combining developments

Robotic MISS and pain relief through BR003 align with and allow integration of the ERAS pillars of optimized surgical technique and optimized pain treatment, respectively. The surgical workflow is streamlined by integrating the surgical intervention with administration of analgesics into a single procedure, as illustrated in Figure 3.

The potential advantages of robotic spine systems and BR-003 resemble different parts of the ERAS guidelines through the same principle: Increasing treatment accuracy to minimize harm to the patient. Together, robotic spine systems and BR-003 can have synergistic effects in spine surgery, where pain arising from minimal tissue damage and a short surgical intervention is precisely treated by a local solution. In turn, patients would need less opioids and are subsequently at lower risk for ORADEs such as dizziness and nausea, allowing them to mobilize and have nutritional intake early after surgery (Figure 3).[17] Precise and effective opioid-reducing analgesia could have beneficial effects beyond the acute postoperative phase. Severe acute postoperative pain, and bone surgery are strong predictors of the development of chronic post-surgical pain.[27,28] Use of prescription opioids is a major predictor of chronic opioid use and opioid abuse.[29,30] These risk factors for chronic pain or opioid use are potentially decreased when BR-003 and robotic MISS are combined.

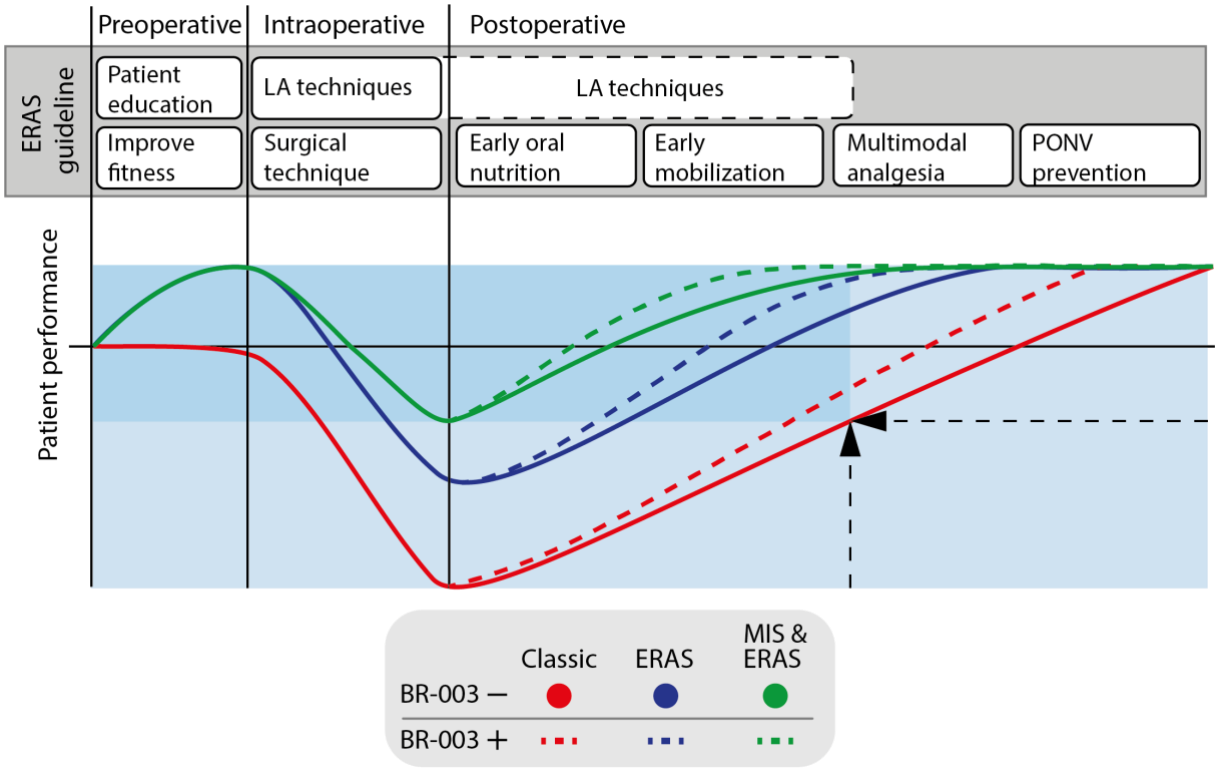

Figure 3 *The envisioned effects of increasing treatment accuracy through integration of minimally invasive robotic surgical approaches and innovative local pain treatment (dashed lines) on patient performance. Employing ERAS principles increases pre-operative patient fitness. Through sophisticated surgical technology, the effect of surgery on patient performance is minimized. Lastly, recovery is enhanced by providing innovative localized pain treatment (BR-003), extending local anesthetic (LA) techniques to the postoperative phase.* MIS *Minimally Invasive Surgery,* ERAS *Enhanced Recovery After Surgery,* LA *Local Anesthetic,* PONV *Post-Operative Nausea and Vomiting.*

Robotic MISS – BR-003 compatibility

BR-003 is compatible with various well-established methods of pedicle screw placement, including free-hand, fluoroscopic-guided and navigation-assisted implantation, and open and minimally invasive approaches. From a percutaneous or minimally invasive approach, it is a small step to implement BR-

003 in robotic-assisted MISS. At present, no compatibility issues are expected between BR-003 and robotic spine surgery systems. However, the exact method and timing of its attachment to a pedicle screw may vary depending on the pedicle-screw/robotic system combination used. The continuous assessment of BR-003 compatibility with robotic systems will be performed by SentryX in collaboration with various pioneers and key opinion leaders in the field of robot-assisted spine surgery.

Conclusion

To conclude, robotic MISS and sustained local pain relief through BR-003 can have a synergistic effect on recovery after spine surgery. By improving treatment accuracy and reducing human operator variability, the combination allows for minimal tissue damage with decreased severity of postoperative pain, which is subsequently precisely treated with local sustained non-opioid analgesics. Lowering surgical invasiveness, postoperative pain and opioid consumption all serve the common cause of inflicting minimal harm and enhancing recovery after surgery. Robotic MISS and local pain relief can increase the efficiency of healthcare through optimal allocation of human resources and shorter hospital stays.

Disclosures

JS, JJV, HJ, FT and BO are paid employees of and own stock in SentryX B.V. AV discloses the following relations directly relevant to this work: Globus Medical: IP royalties, Paid consultant, Stock or stock options; Medtronic: IP royalties, Paid consultant; SentryX: Scientific advisor, stock options.

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