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Effectiveness of continuous wound infusion of 0.5% ropivacaine by On-Q pain relief system for postoperative pain management after open nephrectomy

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Background. Block of parietal nociceptive afferent nerves using continuous wound infiltration with local anaesthetics may be beneficial in multimodal postoperative pain management. The effectiveness of continuous wound infusion of ropivacaine for postoperative pain relief after open nephrectomy was analysed in a prospective, randomized, double-blinded, placebo-controlled trial.

Methods. One hundred and sixty-eight patients were randomized to either 0.5% ropivacaine (ON-Q group) or 0.9% NaCl (control group), using an elastomeric pump which delivered 4 ml h^{-1} over 48 h through two multiholed Soaker® catheters placed between the transverse and the internal oblique muscles and the s.c. space. All patients received a standard postoperative pain management protocol, including patient-controlled analgesic morphine and ketorolac. Outcomes measured over 48 h after operation were visual analogue scale (VAS) and incident (i) VAS pain scores, morphine consumption, and side-effects; time to bowel function recovery; and mean length of hospitalization.

Results. Side-effects were similar between the two groups. VAS and i-VAS pain scores, morphine consumption [11.5 (0.27) *vs* 21.8 (0.37) mg; *P*<0.001], time to bowel recovery [21.8 (0.4) *vs* 33.6 (0.9) h; *P*<0.001], and mean length of hospitalization [2.1 (0.03) *vs* 3.2 (0.1) days; *P*<0.001] were significantly reduced in the ON-Q group. Cost analysis revealed an overall savings of ~273 euros per patient in the ON-Q group.

Conclusions. Continuous surgical wound infusion with ropivacaine improved pain relief and accelerated recovery and discharge reducing overall costs of care.

Optimizing postoperative pain management can be challenging due to surgical factors (type of procedure, surgical approach, and length of surgery), intrinsic patient responses to surgery and pain, and the pharmacologic approaches taken. Hereby, the success of early postoperative discharge is likely coupled with an accurate management of pain and nausea. Multimodal use of adjuvant agents (e.g. local anaesthetics, non-steroidal anti-inflammatory drugs, ketamine, sympatholytics, steroids, and non-pharmacological techniques) which limit the requirements for opioid analgesics may prevent common postoperative side-effects such as ileus, and nausea and vomiting, thus enabling more patients to meet early discharge criteria.

Local anaesthetic wound infiltration is widely recognized as a useful adjunct during multimodal postoperative pain management whether given before operation or perioperatively.[1 2] Owing to a lack of prospective trials investigating the effectiveness of a continuous wound infusion with local anaesthetic after urologic surgical procedures, we sought to determine the efficacy of this technique after a lumbotomic approach to open nephrectomy.

Methods

This prospective, randomized, double-blinded, placebo-controlled study was approved by the Committee for the

protection of Human Subjects in Biomedical Research of the 'Regina Elena' Cancer Institute of Rome, Italy, on the basis of a pilot study, including 25 patients who received active treatments through the device (4 ml h^{-1} of 0.5% ropivacaine): in these patients, the total plasma concentrations of ropivacaine were 1.7 (0.6) and 0.9 (0.3) at 24 and 48 h postoperative checks, respectively. Side-effects in this group were not clinically relevant.

Written informed consent was obtained from all patients before enrolment in the study protocol. Between March 2004 and August 2007, 168 patients were recruited at 'Regina Elena' National Cancer Institute, Rome, Italy. Patients had an American Society of Anesthesiologists physical status I or II, were aged between 47 and 71 yr, and were undergoing open nephrectomy through lumbotomic access.

Exclusion criteria were a history of adverse reactions to local anaesthetics, chronic hepatic disease, obesity (BMI >30 kg m^{-2}), chronic pain, chronic preoperative opioid consumption, psychiatric disorders which would prevent postoperative assessments, and the inability to use a patient-controlled analgesic (PCA) device.

Patients were randomized to receive a continuous surgical wound site infusion of either 0.5% ropivacaine or 0.9% saline delivered by an elastomeric pump (ON-Q PainBuster®, ref. PS6505; I-Flow Corp., Lake Forest, CA, USA) through two multiholed Soaker® catheters. All patients were provided with PCA morphine according to the hospital standard of care for breakthrough pain.

Upon arrival in the preoperative room, an independent pharmacist dispensed a pump filled either with 0.5% ropivacaine (ON-Q group) or 0.9% saline (control group) according to a computer-generated randomization code in all patients. Only the pharmacist was aware of the type of solution to be administered, whereas physicians and attending staff in charge of the patient were fully blinded to the patient's group assignment. Before surgery, all patients, previously informed about PCA, demonstrated their ability to use the device.

Anaesthesia for the surgical case was standardized for all study subjects. Patients were premedicated with midazolam (2.5 mg) and atropine (0.5 mg), given 30 min before the induction of anaesthesia. Induction was performed with propofol (2.5 mg kg^{-1}), cisatracurium (0.15 mg kg^{-1}), and fentanyl (1 μg kg^{-1}). After tracheal intubation, mechanical ventilation with a mixture of 50% O_2 and 50% N_2O was initiated and adjusted to keep the end-tidal carbon dioxide tension between 30 and 35 mm Hg. Maintenance was obtained with sevoflurane 1–1.5% and fentanyl (1–2 μg kg^{-1} h^{-1}). Thirty minutes before awakening, 30 mg of ketorolac was administered to all patients. At the end of procedure, halogenated agents were switched off and 100% O_2 was given with 8 litre min^{-1} fresh gas flow. Residual neuromuscular block was reversed, if needed, with a mixture of atropine and neostigmine.

In all patients, the surgical procedures were performed by the same experienced surgeon, through a 10–15 cm flank incision, between the ninth and the tenth ribs. The borders of the surgical wound were infiltrated with 10 ml of 1% ropivacaine before incision. The intercostal muscle, external and internal oblique muscles, and transversum muscle were dissected and the peritoneum was opened ventrally, exposing Gerota's fascia and, subsequently, the kidney. The ureter and lower pole of the kidney were isolated and subsequently the renal artery and vein were ligated and divided. Finally, the dissection of the upper pole (together with adrenal gland in the case of upper pole tumours) was completed and the ureter was transected. A drain was left in the retroperitoneal space and surgical procedure was completed by closing muscle layers, s.c. space, and skin, respectively, with running sutures.

At the end of the surgical procedure, the surgeon inserted two 20 gauge multiholed Soaker catheters through an introducer needle, ∼2 cm from the lower end of the incision along the full length of the wound (Fig. 1). The first catheter was positioned, after the closure of transverse muscle (deep muscular layer), superior to the transverse muscle and below the internal and the external oblique muscles, which were subsequently closed, separately, with running sutures. The second catheter was positioned in the s.c. space (Fig. 1). Finally, the s.c. space and skin were separately closed with running sutures and catheters and the catheter introducer sites were covered with transparent 'op-site' dressings. Wound infiltration was performed in all patients with a syringe containing 10 ml of 1% ropivacaine regardless of the randomization group. Recovery from anaesthesia and pain management immediately after surgery were identical for all patients. Morphine was administrated with i.v. boluses of 2.5 mg at 5 min intervals, up to a total of 5 mg in all patients and PCA devices (Graseby 9300; Watford, Herts, UK) were set to deliver an i.v. infusion of 1 mg dose with a 15 min lockout time. Protocol variables were measured during 48 h after surgery at 6 h intervals: the first variables measurement was performed at the end of the surgical procedure, immediately after the awakening of the patient and data were recorded as data at time zero. The pre-filled elastomeric pump delivered the randomized solution during the ensuing 48 h with a 4 ml h^{-1} constant flow (2 ml h^{-1} per catheter).

Pain was measured at rest using the visual analogue scale (VAS), 0–10 scale, where 0, none, and 10, very severe, and incident (i) VAS at mobilization (defined as pain experienced when coughing), using the same scale. Morphine consumption was measured on the PCA device.

Time to bowel recovery was defined as the time when first bowel movement was noticed by the patient. All side-effects were monitored and recorded. Nausea and vomiting was recorded as absent or present. The level of sedation was measured using a four-point rating scale (where 1, fully alert; 2, sleepy but easily aroused with verbal stimulation; 3, sleepy but barely arousable; and 4, unconscious patient not answering to contact). Arterial pressure, heart
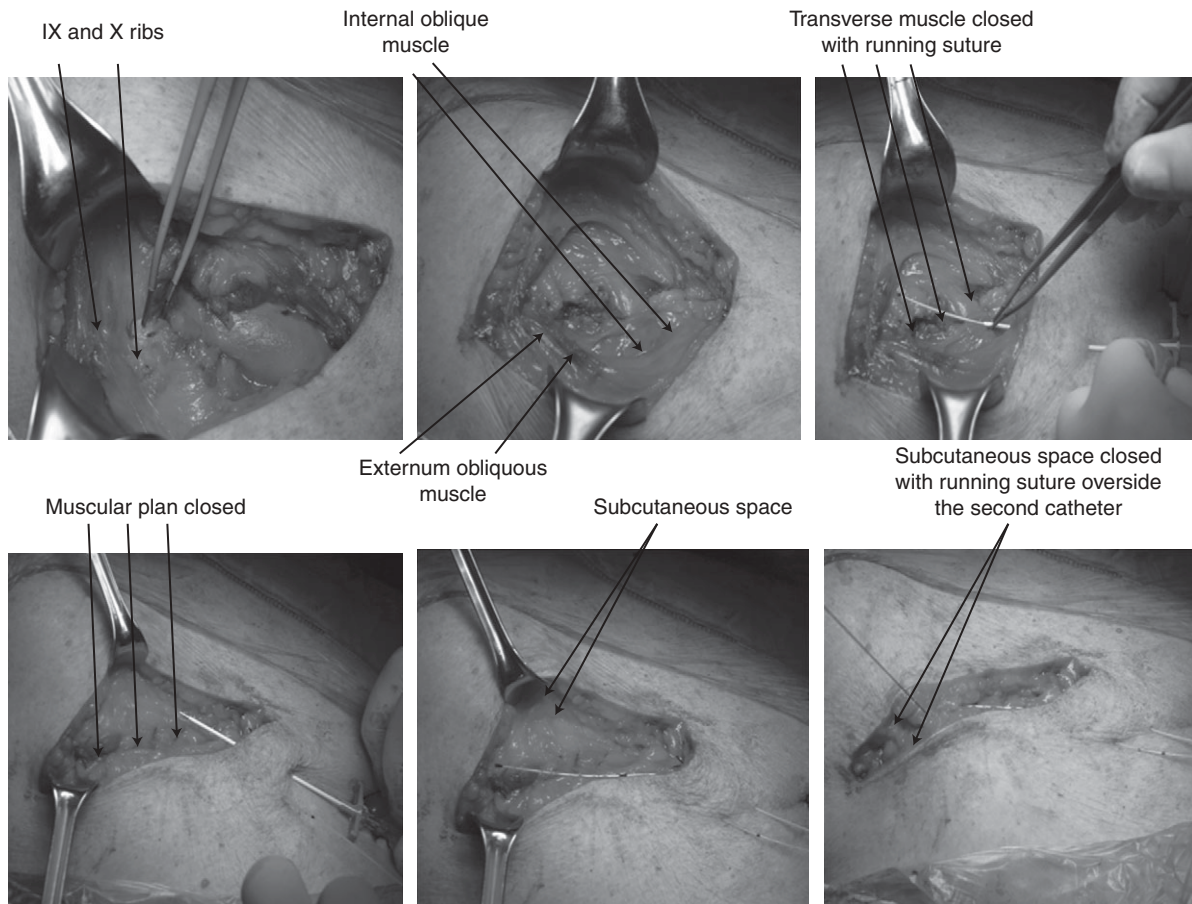
Fig 1 Surgical details showing, step by step, the positioning of two multiholed catheters on On-Q pain Buster.

rate, and breathing rate were recorded together with all variables described above.

Ropivacaine plasma levels were not measured during the study. A preliminary analysis, illustrating ropivacaine plasma levels below the toxicity threshold and the absence of side-effects, was required before submission of the study protocol to the Committee for the Protection of Human Subjects in Biomedical Research of our Institute.

Hospitalization length was recorded. Patients were discharged once they had an absence of fever and anaemia (with a haemoglobin level >10 g dl^{-1}), absence of leucocytosis (defined as white blood cells $>12 \times 10^9$ litre^{-1}), and with clear evidence of absence of nausea or vomiting, with recovered bowel function, and with a VAS score ≤ 2.

Finally, the costs of drugs and devices, operating theatre costs (based on a mean cost per hour), and hospital length of stay costs (based on a mean cost per day calculated by hospital administration on patients treated in our department in the previous year) were recorded and compared between the two groups in a cost analysis.

Statistical analysis

This prospective, randomized, study was designed to identify the effect of a continuous surgical wound infusion with 0.5% ropivacaine on postoperative pain relief after open nephrectomy. Mean VAS was the primary endpoint: assuming a pooled standard deviation of 1 point on the VAS scale, a sample size of 84 patients in each group was required to detect a significant between-group difference, 24 h after operation, of 0.5 point in mean VAS values, with an N risk of 0.05 and an O risk of 0.1. Owing to the duration of this study, no attrition was considered. Pain intensity between-group comparison was performed with repeated-measures (two-way) analysis of variance (ANOVA). The repeated-measures ANOVA was used to test the different trend of continuous variables in the two arms of this study. This analysis allowed us to correctly evaluate repeated observations on patients and to test the effect of experimental treatment and the variables trend along the observation time. Differences between continuous variables at specified time intervals were subsequently evaluated with Student's t-test. Dichotomic variables were analysed using Fisher's exact test. Variables are presented as mean (SE).

The threshold for statistical significance was set at $P<0.05$. Confidence intervals (CI) for main outcomes variables are given.[3] Computerized statistical analysis was performed with the Statistical Package for the Social Sciences software, version 15.0 (SPSS Inc., Chicago, IL, USA).

Results

Overall, 168 patients were enrolled (84 per group). All enrolled patients successfully completed the study and were included in the main analysis. A homogeneous distribution of patients in two groups was achieved by means of randomization, as demonstrated by the absence of significant differences, in terms of age, sex, and weight distribution, between the two groups. No statistically significant differences were observed between the two groups with regard to operating time [mean 78.2 (1.6) *vs* 78.7 (1.3) min; *P*=0.82]. Patient characteristics and intraoperative data are given in Table 1. Pain intensity, both at rest and during coughing, was significantly decreased by the continuous infusion of ropivacaine in the active ON-Q group. A significant group time interaction effect was found on the ANOVA (*P*<0.001) and significant differences (*P*<0.001) were also found on the pairwise comparisons at 24 and 48 h, and for all time intervals but time zero. Morphine consumption was significantly higher in the control group. The mean total morphine consumption over the first 48 postoperative hours was 21.8 (0.37) mg in the control arm and 11.5 (0.27) mg in the experimental arm (Student's *t*-test *P*<0.001). ANOVA showed a significant difference between the two groups in favour of the ON-Q group (*P*<0.001) (Fig. 2).

In reference to side-effects, similar trends between the two groups were observed for arterial pressure, heart rate, and ventilatory frequency. Despite this, significantly higher scores for sedation and nausea and vomiting were observed in the control group. These findings were expected and are likely to be related to increased morphine consumption in this group. Time to bowel recovery was significantly reduced in patients in the ON-Q group [21.8 (0.4) *vs* 33.6 (0.9) h; *P*<0.001] and time to discharge [2.1 (0.03) *vs* 3.2 (0.1) days; *P*<0.001].

These statistical data are summarized in Tables 2 and 3. We then performed an overall cost analysis, beginning with the cost of morphine consumption by PCA (1.50 euros per patient in the control group and 0.79 euro per patient in the ON-Q group) and the cost of operating theatre (500 euros per hour; mean operating times were 78 min in both groups). These items did not impact the financial savings in favour of either of the two groups. The cost of the ON-Q PainBuster devices (280 euros per device) and the cost of ropivacaine administered to patients of the ON-Q group (96 ml of ropivacaine 1% used for each

patient; 272 euros per patient) totalled 552 euros. The cost of saline solutions and devices used for patients of the control group was not included in cost analysis.

Finally, the cost related to hospitalization was evaluated according to data obtained by the hospital administration, calculated as mean cost per patient per day of hospital staying in our department in the last year of the current trial. With an estimated mean cost per day of 750 euros, hospitalization costs were 1575 euros (mean hospital stay 2.1 days) for patients of the ON-Q group and 2400 euros (3.2 days) for patients in the control group, resulting in a difference between the two groups of 825 euros in favour of the ON-Q group. Allowing for the cost of the pump and the ropivacaine, the ON-Q group realized an overall savings of ~273 euros. Calculated over the active cohort group of 84 patients, the savings on the protocol patients would have amounted to 22 932 euros.

Discussion

Multimodal analgesia is a rational approach to treat various components of postoperative pain (tissue injury and nociceptive stimulation and subsequently 'central way' activation). The combined use of different analgesic techniques that span different phases of analgesia leads to further decreases in pain, utilizing lower dosages, thus avoiding or reducing the risk of adverse drug effects.[4] There is evidence in the literature that a multimodal approach to postoperative pain provides better results when used along with 'pre-emptive analgesia'. These trials have demonstrated greater analgesic effectiveness when the drug is administered before pain onset.[5] Data from animal studies provide further support of these hypotheses. These studies have shown that parietal pain may sensitize spinal cord neurones to visceral colonic pain,[6] and these data suggest that the block of parietal afferents may reduce spinal dorsal horn neurone sensitization, consequently providing analgesia over the duration of wound infusion.[7] Hopf and colleagues highlighted how postoperative pain affects the inflammatory response and increases catecholamine release leading to a reduced wound perfusion and oxygenation. Consequently, wound infiltration with local anaesthetics may provide pain control with the added benefit of increased wound perfusion and oxygenation enhancing wound healing.[8]

One time bolus injections of local anaesthetics can provide narcotic-limiting pain relief for 4–8 h after operation. However, the duration of analgesia is brief and does not provide long-term benefits in terms of pain control or narcotic-limiting outcomes. The time-limited effect of a single bolus administration of a local anaesthetic has been improved through continuous surgical wound infusion techniques using multiholed soaker type catheters, positioned by the surgeon at the end of procedure. A systematic review of randomized controlled trials confirmed the

Table 1 Patient characteristics and intraoperative data

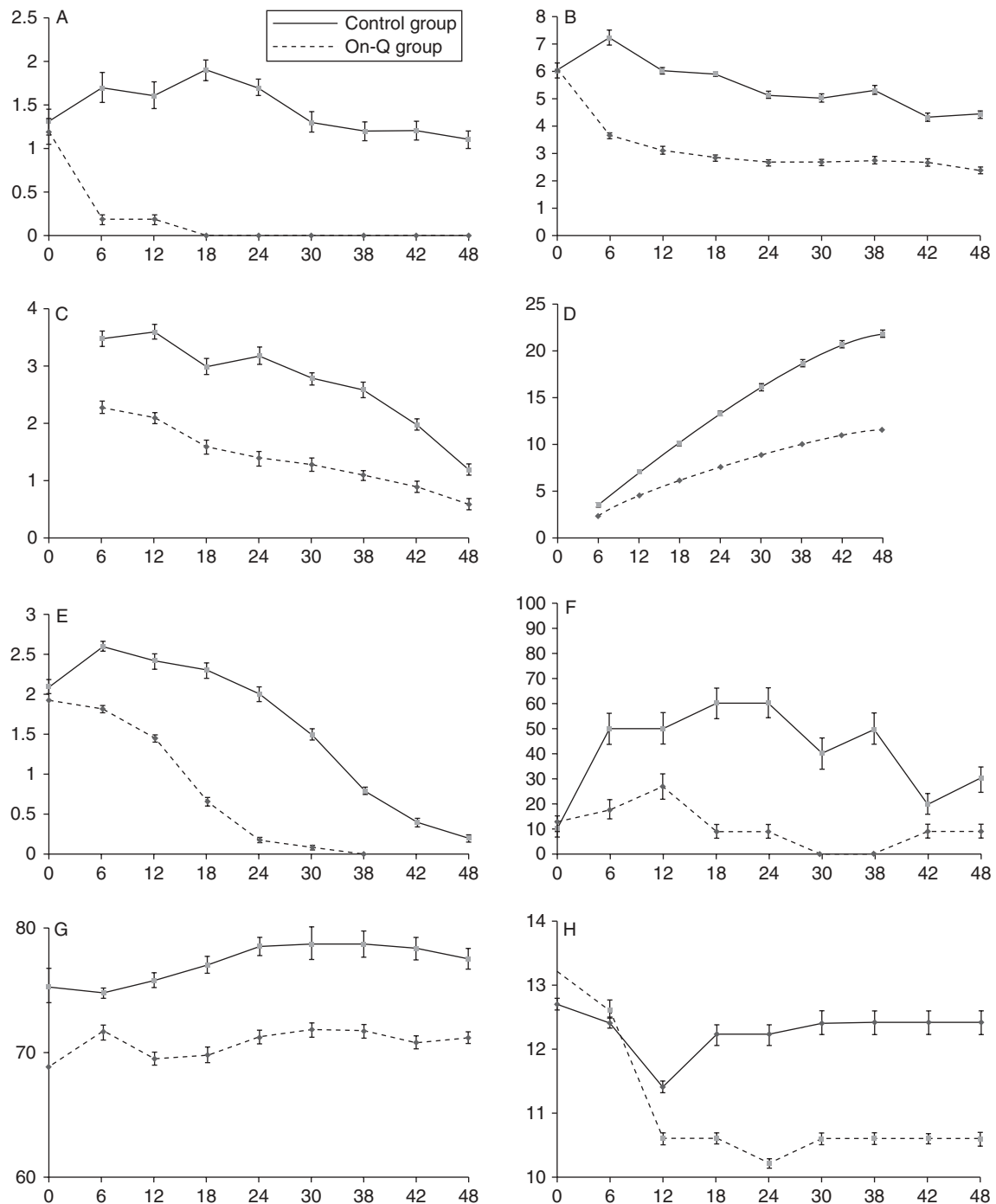|	Ropivacaine group (*n*=84)	Placebo group (*n*=84)
Mean age (range) (yr)	58.7 (45–71)	60.2 (47–76)
Sex (male/female)	32/52	32/52
ASA physical status (I/II)	37/47	41/43
Mean BMI (SD) (kg m^{-2})	26.3 (2.9)	26.6 (3.2)
Mean operating time (SD) (min)	78.2 (1.6)	78.6 (1.3)
Mean length of surgical incision (SD) (cm)	12 (2.1)	11.8 (2.5)

Fig 2 Main variables analysed. (A) mean VAS score/postoperative hours; (B) mean i-VAS score/postoperative hours; (C) mean morphine consumption (mg) at each time interval; (D) cumulative morphine consumption(mg)/postoperative hours; (E) sedation score/postoperative hours; (F) percentage of patients with nausea–vomiting/postoperative hours; (G) mean heart rate at each time interval; and (H) breathing rate at each time interval.

benefits and the safety of this technique when applied in several major painful procedures, such as cardiac, thoracic, major gynaecologic, or spinal surgery. The authors highlighted how the effectiveness of this technique might be different according to the type of surgery and the proper placement of the catheters.[9] The effectiveness of single injections or continuous infiltration of the surgical area with local anaesthetics depends in part on the level of

tissue where the infiltration takes place. Subcutaneous infiltrations may not improve postoperative pain scores, although they do impact opioid consumption.[10] [11] However when compared with subfascial injections, the deeper infiltration results in better efficacy.[12] This was also shown in a comparative study conducted in Denmark where patients underwent inguinal herniotomy, subfascial injections of lidocaine were compared with s.c. injections

Table 2 Statistical significance and CI of main variables

'End point' variables	Control (mean score)	OnQ (mean score)	95% CI	Student's *t*-test *P*-values
VAS at 24 h	1.7	0	1.5–1.9	<0.0001
VAS at 48 h	1.1	0	0.9–1.3	<0.0001
i-VAS at 24 h	5.1	2.6	2.2–2.7	<0.0001
i-VAS at 48 h	4.4	2.4	1.7–2.4	<0.0001
Morphine consumption at 24 h	13.3	7.5	5.1–6.5	<0.0001
Morphine consumption at 48 h	21.8	11.5	9.4–11.2	<0.0001

Table 3 Statistical significance of ANOVA for each variable, showing the treatment effectiveness and variables trend along the observation time

Repeated-measures ANOVA	On-Q *vs* control	On-Q *vs* control along time
VAS	<0.001	<0.001
i-VAS	<0.001	<0.001
Morphine consumption	<0.001	<0.001
Sedation	<0.001	<0.001
Mean arterial pressure	NS	NS
Heart rate	<0.001	<0.001
Breathing rate	<0.001	<0.001
Nausea and vomiting	<0.001	<0.001
Time to bowel recovery	<0.001	<0.001

(1.0% 10 ml). The injections were given in the wound after operation through a catheter placed in the respective layer intraoperatively. In the s.c. group, significant greater reductions in postoperative pain scores after coughing, mobilization, and during rest in the subfascial group were obtained. The time to first request of additional analgesics was sooner in the s.c. group in this study.[13] The efficacy of subfascial placement has been show in numerous studies with the ON-Q device in procedures such as sternotomy, inguinal hernia, and radical prostatectomy. A comparison between the two placements has not yet been performed.[14–16] In a recent study investigating the effectiveness of a continuous preperitoneal infusion of ropivacaine, Beaussier and colleagues[17] illustrated the difference in efficacy of the technique with regards to the positioning of the catheter. They hypothesized that although the block of parietal nociceptive inputs to the superficial layer of the abdominal wall can be reached by a s.c. placement of the catheter, this superficial placement would be ineffective in controlling pain from surgical injuries to both the fascia of the abdominal muscles and peritoneum. Shallow placement of the catheter may be the primary reason for lack of efficacy of this technique after open abdominal surgery.[18] The study performed by Wu and colleagues[19] after prostatectomy further illustrates the need for deep placement with proper concentration and volume of local anaesthetic.

Endpoints of the current study were: first, to evaluate the impact of this treatment on postoperative pain, directly, by questioning patients using a specific pain score and, indirectly, by measuring postoperative morphine consumption and morphine-related side-effects and, second, to evaluate, with a cost analysis, if the hypothesized faster recovery in patients treated with a continuous surgical

wound infusion of ropivacaine would lead to a financial savings due to reduced hospitalization time. In the current study, we observed a significant benefit in the experimental arm in terms of improved pain management, reduced morphine consumption, and accelerated patients recovery: pain at rest was absent at 24 h check in the experimental arm and pain score when coughing is half that observed in the control arm (both Student's *t*-test and ANOVA test <0.001); the mean total morphine consumption over the first 48 postoperative hours was 21.8 (0.37) mg in the control arm and 11.5 (0.27) mg in the experimental arm (Student's *t*-test *P*<0.001); time to bowel recovery was significantly reduced in patients in the ON-Q group [21.8 (0.4) *vs* 33.6 (0.9) h; *P*<0.001]; and time to discharge [2.1 (0.03) *vs* 3.2 (0.1) days; *P*<0.001]. These data support our hypotheses and thereafter the main endpoint of the study.

Control of postoperative pain should be of interest to surgeons, anaesthetists, and hospital administrators alike. Optimal management of postoperative pain, faster recovery and discharge of patients after major surgery, and length of hospital stay and a fast turn-over of patients leading to financial savings are 'the goal' for anaesthetists, surgeons, and hospital administrators, respectively. Adequate pain management increases mobility and decreases risk of development of deep venous thrombosis and pneumonia. Systemic narcotics provide generalized analgesia but may be accompanied by side-effects such as respiratory depression, excessive sedation, pruritus, constipation, ileus, nausea, and vomiting. This may lead to decreased mentation, reduced mobility, and a slower return to normal activities.[8] The emerging role of continuous wound infiltration with local anaesthetics as part of multimodal analgesia approach after major surgery is based on the recognition of the important role played by parietal nociceptive afferent nerves in the overall production of pain, and in the pathophysiologic repercussions induced by surgery.[11]

To our knowledge, this is the first study investigating the effectiveness of continuous infusion of 0.5% ropivacaine after open nephrectomy *via* lumbotomic access. Lumbotomy is a highly painful access to retroperitoneal space, preferred by many urologists in order to prevent opening the peritoneal space through a midline incision. Furthermore, this access provides a direct window to the kidney, without the need of mobilizing bowel or other viscera. The main drawback of this access is its highly painful nature. On the other hand, a midline incision approach requires an extended (often xyphoid-pubic) incision, at least two-fold longer than lumbotomic incision (25–30 *vs* 10–15 cm). Therefore, midline incisions could be considered an overly invasive approach for this procedure, producing a similar level of postoperative pain compared with lumbotomy when considering the length of the incision and the important contribution of the peritoneum to postoperative pain intensity.[11] Our hypothesis that improving pain management could lead to accelerated discharge, and to financial savings as a result of reduced

costs of hospitalization, has been confirmed by the findings of this study. Patients who received a continuous surgical wound infusion of ropivacaine after surgical treatment had improved outcomes in terms of pain relief, lower morphine consumption, and accelerated recovery and discharge. Earlier discharge led to financial savings, as the total costs of ON-Q device and ropivacaine in patients of the ON-Q group were lower than costs of hospitalization in patients of the control group.

Clearly, the limitation of this analysis is the lack of detailed analysis of each cost required by a single patient in the postoperative setting. The mean daily cost of hospitalization was obtained in uncomplicated patients and met the same inclusion and exclusion criteria as the patients enrolled in the study (ASA score I or II, BMI <30 kg m^{-2} with subsequent absence of complications after surgical procedure). The goal of this analysis was to prove that the continuous infusion of ropivacaine by the ON-Q device would provide improved postoperative recovery outcomes without extra costs. Further studies in postoperative pain management should look at the use of two catheters placed in different sites in order to manage different components of overall pain. These placements should be compared with the use of a single catheter placed, alternatively, in s.c. space and into the muscular plane. Future prospective trials are also needed to compare the analgesic effectiveness of ropivacaine, with its lower toxicity risk profile, to other 'low cost' local anaesthetics. Finally, our results need to be validated by further analyses in a multicentre experience.

In conclusion, the efficacy of a continuous surgical wound infusion with local anaesthetics, and the recognized role played by nociceptive receptors at the various anatomic planes, lead us to test the effectiveness of using two multiholed Soaker catheters placed in the s.c. space, muscular plane, and peritoneal layer after radical nephrectomy through lumbotomic access. This therapy proved to be an effective component of a multimodal approach to postoperative pain management and resulted in decreased pain and narcotics, and a cost savings due to accelerated recovery and early discharge of patients.

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