

THE ROLE OF SPINAL ANAESTHESIA WITH AND
WITHOUT INTRATHECAL OPIOID COADMINISTRATION
IN IMPROVING ONCOLOGIC OUTCOMES AFTER
ENDOSCOPIC TRANSURETHRAL CANCER SURGERY

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Abstract

Spinal anaesthesia (SA) (compared to general) improves postoperative oncologic outcomes in transurethral resection of the bladder tumour (TURBT) for non-muscle invasive bladder cancer (NMIBC). Intrathecal coadministration of opioids does not affect NK cells function, and improves postoperative opioid sparing as well. There are no comparative data on oncologic outcomes of SA with/without intrathecal opioid in TURBT, which is the aim of our study.

Seventy ASA I-III patients with NMIBC, aged ≥ 43 (range 43–90), who underwent one or more TURBT under SA were examined retrospectively. Of them, 36 received levobupivacaine 15 mg (L group) and 34 levobupivacaine 12.5 mg + fentanyl 12.5 mcg (LF group) intrathecally. All patients received scheduled Paracetamol 1.0 g/6 h, optional NSAIDs and as needed Tramadol as well. Data regarding demographics, ASA and CCI scores, analgesics consumption, urethrotomies, tumour-related factors (size, number, grade, stage, prior disease-recurrence, adjuvant therapy), tumour risk (low, intermediate, high), oncologic outcomes (recurrence rate/free time after TURB during the regular cystoscopy every 3 months/first year, every six months thereafter) were explored as well. LF patients were older, with less analgesics consumption and with a tendency towards longer recurrence-free time compared to L patients ($p = 0.074$). The recurrence at three months along with prior and new

disease-recurrences comprise our minority ($n = 27$) with aggressive course of the disease. Among the rest the majority, LF subgroup ($n = 19$) had lower recurrence rate than L subgroup ($n = 24$) ($p = 0.03$). As part of multimodal analgesic strategy, SA with intrathecal opioid coadministration may play a significant complementary role regarding oncologic outcomes after TURBT for NMIBC.

Key words: spinal anaesthesia, intrathecal opioids, TURBT, oncologic outcomes

Introduction. Bladder cancer is a common socially significant disease. More than 95% of bladder cancers are urothelial carcinomas, and non-muscle-invasive bladder cancer (NMIBC) accounts for 75–80% of urothelial carcinomas, including bladder tumours confined to the mucosa (stage Ta, carcinoma in situ) or sub-mucosa (stage T1) [1]. With regard to Europe, in 2012 it was estimated there were 118 000 new cases and 52 000 deaths. Expenditures have been estimated at around € 4.9 billion in the European Union (EU) [2].

The average age at diagnosis of bladder cancer is 73 years [3], and due to the strong association with cigarette smoking, many patients undergoing treatment are elderly with multiple comorbidities and poor pulmonary function [4]. Spinal anaesthesia (SA) is often preferred in this group of patients, where general anaesthesia may carry increased risk of cardiorespiratory complications. Moreover, SA (compared to general) improves postoperative oncologic outcomes in transurethral resection of the bladder tumour (TURBT) for NMIBC [5, 6]. Intrathecal coadministration of opioids does not affect NK cells function [7], and improves postoperative opioid sparing as well [8]. There are no comparative data on oncologic outcomes of SA with/without intrathecal opioid in TURBT, which is the aim of our study.

Materials and methods. Seventy ASA I-III patients with NMIBC, aged ≥ 43 (range 43–90), who underwent one or more TURBT under SA were examined retrospectively. Of them, 36 received levobupivacaine 15 mg (L group) and 34 levobupivacaine 12.5 mg + fentanyl 12.5 mcg (LF group) intrathecally. All patients received scheduled Paracetamol 1.0 g/6 h, optional NSAIDs and as needed Tramadol as well. Data regarding demographics, ASA and CCI scores, analgesics consumption, urethrotomies, tumour-related factors (size, number, grade, stage, prior disease-recurrence, adjuvant therapy), tumour risk (low, intermediate, high [9]), oncologic outcomes (recurrence rate/free time after TURBT during the regular cystoscopy every 3 months/first year, every 6 months thereafter) were explored as well. Time to recurrence was calculated from the date of operation to recurrence. Tumour recurrence after TURBT was evaluated using the Kaplan–Meier method [5].

Intravenous (i.v.) infusion of 10 mL/kg of Riger solution was given before initiation of the SA. Insertion of the spinal needle was undertaken in aseptic conditions using a 25-G Quincke needle at the lumbar L3–L4 interspace with midline or

paramedian approach. If the tumour was located laterally in the bladder, an additional endoscopic injection of local anaesthetic into the tumour base was delivered as an obturator nerve block. The operation was started 15 min after the initiation of spinal anaesthesia if the level of sensory block had reached T10 or above. Adverse effects of intrathecal opioids, like hypotension, bradycardia, respiratory depression, nausea, vomiting, shivering, and pruritus, as well as adverse effects of the extended TURBT, like continuous (24–72 h) postoperative bladder irrigation, catheter-related bladder discomfort (CRBD), significant postoperative pain VAS ≥ 4 at rest and ≥ 6 during movement and physiotherapy [10], and limitation of implementing physiotherapy for early mobilization and rehabilitation of voiding dysfunction through perineal muscles contractions were recorded accordingly. All statistical analyses were performed at $\alpha = 0.05$.

Results. The demographic, clinical and treatment data of the study are depicted in Table 1. LF patients were older, with less analgesics consumption and with a tendency towards longer recurrence-free time compared to L patients ($p = 0.074$) (Table 1, Fig. 1). The recurrence at 3 months along with prior and new disease-recurrences comprise our minority ($n = 27$) with aggressive course of the disease. Among the rest majority, LF subgroup ($n = 19$) had lower recurrence rate than L subgroup ($n = 24$, $p = 0.03$, Fig. 2).

T a b l e 1

Participant demographic, clinical and treatment data (mean $\pm$ SD, unless otherwise specified); ASA (American Society of Anesthesiologists); CCI (Charlson Comorbidity Index); BCG (Bacillus Calmette–Guerin)

	Group L ($n = 36$)	Group LF ($n = 34$)	p
Age (years)	64.7 $\pm$ 11.6	70.8 $\pm$ 10.4	0.025
Gender (Male/Female)	26/10	23/11	0.676
ASA (1/2/3 scores)	9/17/10	3/20/11	0.198
CCI (0–2/ ≥ 3 scores)	22/14	21/13	0.955
Tumour size (< 1 cm/1–3 cm/> 3 cm)	17/16/3	9/18/7	0.127
Tumour number (single/multiple)	24/12	19/15	0.354
Tumour stage (Ta/T1/Tis)	18/16/2	10/22/2	0.203
Tumour grade (G1/G2/G3/none)	11/13/10/2	12/12/9/1	1.000
Tumour risk (low/intermediate/high)	5/11/20	2/6/26	0.197
Tumour recurrence (no/ ≤ 6 / > 6 months)	16/15/5	19/15/0	0.074
Prior disease recurrence (yes/no)	12/24	13/21	0.669
Urethrotomy (yes/no)	10/26	7/27	0.483
BCG therapy (yes/no)	13/23	6/28	0.086
Chemotherapy (yes/no)	9/27	7/27	0.660
Opioids (yes/no)	17/19	8/26	0.039
NSAIDs (yes/no)	32/4	23/11	0.030
Simple analgesics (yes/no)	34/2	23/11	0.043

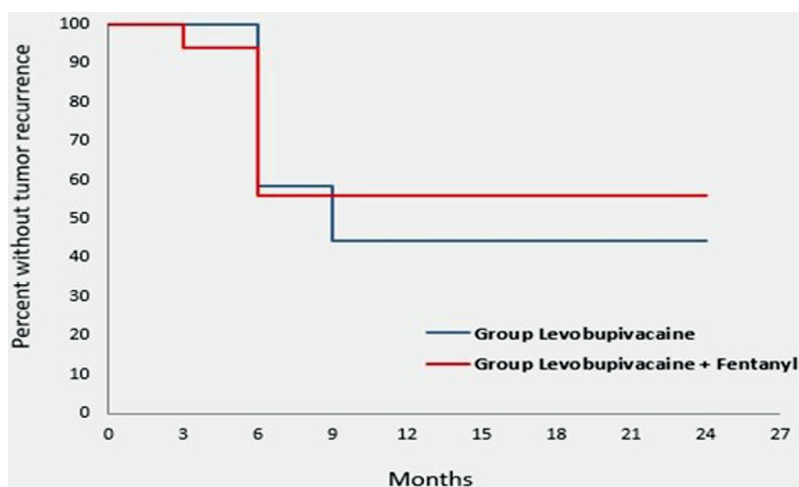


Fig. 1. Kaplan–Meier curves of percentage of patients without tumour recurrence (whole-group comparison, $n = 70$, $p = 0.074$)

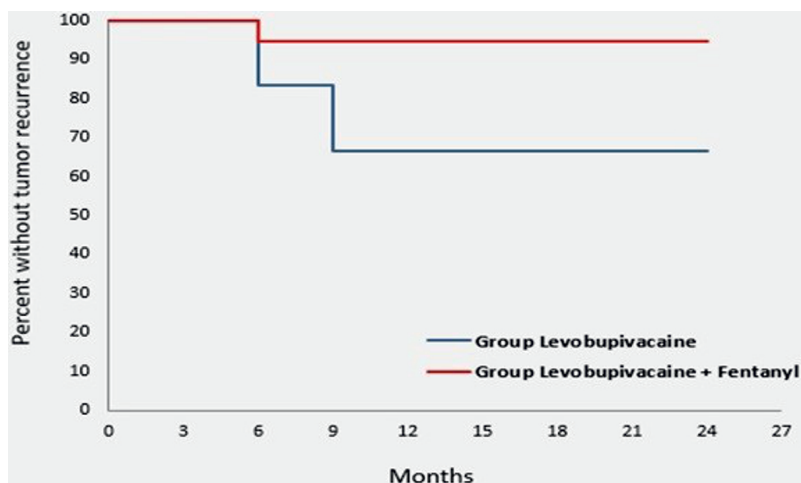


Fig. 2. Kaplan–Meier curves of percentage of patients without tumour recurrence (in subgroups without aggressive course of the disease, $n = 43$, $p = 0.03$)

Adverse effects after implementing SA (with and without fentanyl) like hypotension, bradycardia, respiratory depression, nausea, vomiting, shivering, and pruritus are shown in Table 2 and were statistically similar in the two groups.

Adverse effects of the extended TURBT, like transvesical obturator nerve block, continuous postoperative bladder irrigation, CRBD, significant postoperative pain and limitations of early physiotherapy are shown in Table 2 as well. Incidences of CRBD, of postoperative pain and of postponing postoperative physiotherapy were statistically higher in L group compared to LF group.

T a b l e 2

Adverse effects of spinal anaesthesia (with and without intrathecal opioid coadministration) and TURBT after extensive resections (large tumours, multifocality, multiple resections with a larger or scarred traumatic surface)

	Group L ($n = 36$)	Group LF ($n = 34$)	p
Anaesthesia adverse effects (yes/no)			
Hypotension	10/26	5/29	0.190
Bradycardia	9/27	14/20	0.157
Respiratory depression	0/36	1/33	0.298
Nausea and vomiting	2/34	3/31	0.513
Shivering	8/28	3/31	0.137
Pruritus	0/36	1/33	0.298
Surgery adverse effects (yes/no)			
Transvesical obturator nerve block	8/28	6/28	0.601
Continuous postoperative bladder irrigation	14/22	15/19	0.673
Catheter-related bladder discomfort (CRBD)	20/16	9/25	0.014
Higher level of postoperative pain	13/23	5/29	0.046
Limitation of early physiotherapy	19/21	8/26	0.010

Discussion. Our data (Table 1, Fig. 1, 2) are in line with the proposed vision of the management of NMIBC [11], as well as with the oncologic outcomes reported by others [5, 6]. A good outcome for patients with NMIBC depends on multiple factors, including not just the characteristic of the cancer but also the technology available, the anaesthetic approach, the skill of the surgeon and multidisciplinary support [11]. Patients with the poorest prognosis also warrant the most aggressive treatment [11], with a focus on optimizing ongoing immunotherapy or chemotherapy and choosing timely radical cystectomy rather than on anaesthetic adjustments.

In light of the COVID-19 pandemic and the risk of aerosol-generating events during general anaesthesia, SA presents significant advantages. The European and American Societies of Regional Anaesthesia [12], have advised that regional anaesthesia should be preferred over general anaesthesia wherever possible. And our data are more relevant than ever in the context of the Covid 19 pandemic.

Inhalational anaesthetic agents suppress NK cell activity but the effect does not last after the surgery. The suppression of NK cell activity after the surgery is likely due to the surgical stress, which may be blocked via SA. Thereby, regional anaesthesia compared to general anaesthesia may result in lower tumour recurrence due to mechanisms related to NK cell activity [13]. Thus regional anaesthesia, potentially by minimizing the use of volatile anaesthesia and opioids, is associated with a reduction in perioperative immunosuppression and maintenance of the functionality of anticancer immune cells [6]. Another protective

effect of the SA was found in reducing the lymphatic flow (in lymphatic vessels and nodes) through a likely mechanism of sympathectomy in patients with cervical and prostate cancer for brachytherapy [14]. In our study the combination of levobupivacaine with fentanyl reached a sufficiently higher level of sensory block because levobupivacaine plus fentanyl solution is more hypobaric than the pure levobupivacaine solution [15]. Our regional anaesthetic technique provides an effective sympathetic block (at T9–L1 chain) that can decrease lymphatic flow, while operative stress and general anaesthesia increases sympathetic stimulation and promotes the lymphatic flow [14].

With regards to the advantages and disadvantages of implementing SA with and without intrathecal fentanyl (Table 2), others suggest that addition of 25 mcg fentanyl to low-dose bupivacaine significantly decreases the incidence of shivering, as well as increases the pruritus during SA in elderly patients [16]. We could not reach significance in both directions probably due to half the lower dose of implemented intrathecal fentanyl (12.5 mcg) in our study.

Our findings after extended TURBT in LF patients (Table 2) suggest good tolerability of continuous postoperative bladder irrigation (a factor associated with a lower early recurrence rate [17]), with significantly less CRBD, pain and delaying early physiotherapy. The latter suggest the role of LF combination to the effectiveness of enhanced recovery after urological surgery in its part related to the need for more evidence concerning intraoperative anaesthetic protocols, postoperative analgesia and early postoperative mobilization as well [18].

As shown in Table 1, more adult patients received levobupivacaine with fentanyl in order to have a mild haemodynamic response to SA. Thus our non-randomized administration of intrathecal opioid cannot exclude a potential for patient selection bias, which is a limitation of the study design.

Conclusions. As part of multimodal analgesic strategy, SA with intrathecal opioid coadministration may play a significant complementary role regarding oncologic outcomes after TURBT for NMIBC. The type, grade, stage, and location of tumour do matter.

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