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ORIGINAL RESEARCH

The Addition of Intrathecal Clonidine to Reduce Medication-Related Side-Effects in Cancer Pain: A Retrospective Cohort Study

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Objective: Compared to conventional medical management, targeted drug delivery provides superior cancer pain management with fewer side-effects and potentially improved survival. Intrathecal (IT) clonidine has been used off-label to improve analgesia in patients with cancer pain, but evidence regarding safe dosing in this patient population is limited. This study evaluates the impact of adding IT clonidine on pain, opioid consumption, and the prevalence of medication-related side-effects. It also provides initial dosing recommendations for cancer pain.

Materials and Methods: This was a retrospective chart review conducted at a single academic cancer center. Medical records between 2012 and 2022 were queried for patients who had an intrathecal pump (ITP). Patients' charts were reviewed prior to starting IT clonidine, at the IT clonidine start date, at 1–3 months follow-up, and at over three months follow-up. Primary outcomes included the visual analog scale (VAS) score and daily systemic morphine milligram equivalents (MME). Secondary outcomes included IT or systemic medication side-effects and the daily doses of concurrent IT opioids and local anesthetic (LA).

Results: Eighteen patients were included. No significant change in VAS or systemic MME was observed at follow-up after starting IT clonidine. Median daily IT bupivacaine and opioids with or without patient-controlled boluses significantly rose by the first follow-up; by the second follow-up, only IT opioids were elevated. There was a trend towards a lower prevalence of medication-related side-effects across follow-up periods. On post-hoc logistic regression analysis, IT clonidine dosing was the sole significant predictor of side-effect prevalence. Higher IT clonidine dosing was associated with a lower likelihood of side-effects. Initial IT clonidine doses of 40–60 mcg/day were associated with a 50–75% reduced probability of side-effects.

Conclusion: While its role in reducing pain and systemic opioids is complex, IT clonidine may have a beneficial role in mitigating medication-related side-effects from systemic opioids, IT opioids, or LA for cancer pain. IT clonidine may be safely initiated at doses of 40–60 mcg/day for this indication.

Keywords: intrathecal pump, intrathecal clonidine, morphine milligram equivalent, MME, visual analog scale, VAS, cancer pain

Introduction

Cancer pain can be incredibly difficult to manage. More than 30% of patients with metastatic or advanced-stage cancer have moderate-to-severe pain, and in about 10–30% of patients with limited life expectancy, adequate pain relief is not achieved with the World Health Organization's traditional analgesic ladder.[1–3] For these patients, targeted drug delivery (TDD) via the intrathecal pump (ITP) has been game-changing in terms of providing pain relief. The use of TDD for cancer pain has gained substantial popularity since the 1980s.[4] While the cost-effectiveness of TDD for refractory cancer pain compared to conventional medical management is still a matter of debate, it has been shown to provide better pain control, fewer side-effects, and potentially better survival in this patient population.[5,6]

Since its inception, TDD has witnessed an expansion of available medications to fine-tune therapy. While morphine and ziconotide continue to be the only FDA- and EMA-approved intrathecal medications for pain management, other

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opioids including hydromorphone and fentanyl, as well as adjuncts such as local anesthetics (bupivacaine) and alpha-2 agonists (clonidine) have been utilized off-label in cases of morphine or ziconotide-related side-effects or to offset systemic opioid-related side-effects. Clonidine is an alpha-2 agonist whose analgesic benefit is linked to activation of monoamine-dependent endogenous pain modulating pathways in the spinal cord, inhibition of the locus coeruleus in the brain, and anti-inflammatory effects through inhibition of NF-kB- and p38-mediated release of cytokines including TNF-alpha, IL1, and IL6. [3,4,7–9] One of the earliest uses of intrathecal (IT) clonidine was in 1986, in combination with an IT opioid in a patient with terminal abdominal cancer pain.[10] Nowadays, clonidine is favored particularly for neuropathic pain, and has been incorporated into TDD either as a secondary alternative to local anesthetics (LA), or as a tertiary add-on to opioid/LA combinations.[11–13] Clonidine's potential side-effects - most notably hypotension, bradycardia, and sedation - have limited its adoption as first-line IT therapy for refractory pain.[4,13] It should be noted, however, that IT clonidine has been suggested to also have a pressor effect at higher IT doses when administered as a monotherapy for postoperative analgesia after C-section. [14]

There is a relative paucity of evidence for the optimal utilization of IT clonidine specifically for cancer pain. The Polyanalgesic Consensus Conference (PACC) recommendations for the initiation of TDD by pain type (nociceptive vs neuropathic) and malignancy status (cancer vs non-cancer) have remained the most researched, comprehensive, and expert consensus-based.[3,4,6] That said, they are non-specific in terms of decision-making regarding the initiation of adjuvant IT medications for cancer pain. While the PACC guidelines do recommend dose ranges for IT clonidine bolus trial, long-term continuous delivery, and maximum concentrations and daily doses, those doses are not specific to cancer pain.[4] Additionally, they recommend clonidine as a second- or third-line agent. Meanwhile, perhaps the most comprehensive literature on IT clonidine dosing specifically for refractory cancer pain to date comes from Mastenbroek et al in a small, retrospective study of 9 patients undergoing multimodal TDD with morphine, bupivacaine, and clonidine tri-drug combination.[15] The authors offer starting clonidine infusion rates of 72–144mcg/day alongside morphine and bupivacaine, as well as suggestions for patient-administered bolus strategies and a workflow for side-effects monitoring and dose adjustment.[15]

In this study, we offer a retrospective analysis of IT clonidine therapy initiation strategies across a cohort of 18 patients that is generalized across multiple IT opioids and either with or without the co-administration of IT LA. A common approach to TDD is to start with first-line therapies of opioid with or without LA. However, in the oncologic population, pain medication requirements are constantly increasing due to progression of disease and/or treatment-related side-effects, thus increasing the likelihood of opioid-related side-effects. Our specific objective was to evaluate the impact of adding IT clonidine on reported pain intensity, utilization of opioids, and the prevalence of patient-reported medication side-effects. Additionally, we wanted to expand the best practice literature base for the initiation of IT clonidine for cancer pain within the context of a multi-drug TDD regimen.

Materials and Methods

This was a retrospective chart review conducted at a single academic cancer center. A database search of electronic medical records between 2012 and 2022 focused on patients who had an ITP and were seen by our pain management service. Patients were included if they were 18 years or older, had pain from active cancer, had IT clonidine added to an existing ITP regimen, and had at least one in-hospital evaluation before starting IT clonidine. Patients' charts were reviewed prior to starting IT clonidine, at the IT clonidine start date, at 1–3 months follow-up, and at over three months follow-up. Primary outcomes included visual analog scale (VAS) pain scores and daily systemic morphine milligram equivalents (MME). Secondary outcomes included the presence of any IT or systemic medication-related side-effects (including hypotension, bradycardia, sedation, numbness, and urinary retention among others) at follow-up, and the daily doses of concurrent IT opioids and LA. Patients with any missing outcomes data were excluded in order to minimize the risk of reporting bias. This study was approved by the Memorial Sloan Kettering Cancer Center Institutional Review Board (MSKCC IRB) with waiver of informed consent.

Statistical Methods

The R software package was used for all statistical analysis (R-project.org). Following assessment for normality using the Shapiro–Wilk test, non-parametric statistics were chosen to describe the cohort and assess changes in VAS, systemic MME, IT

or systemic medication-related side-effects, and daily doses of concurrent IT opioids and LA relative to baseline evaluation. The median and interquartile range (IQR) were used to describe the cohort. The one-tailed Wilcoxon rank-sum test was used to assess changes in VAS and systemic MME relative to the IT clonidine start date. For all other comparisons, the two-tailed Wilcoxon rank-sum test was used. For all comparative analyses, the alpha cutoff was set to $\alpha<0.05$ for statistical significance. Post-hoc logistic regression analysis was used to predict the prevalence of any side-effects.

The Strengthening The Reporting of Observational Studies in Epidemiology (STROBE) recommendations for cohort studies were referenced for the purposes of writing this paper.

Results

Of the one-hundred and seven patients total reviewed, eighteen patients were included based on the inclusion criteria and having data at all follow-up time points. Of the 18 patients that underwent full analysis, 44% were male and the mean age at the start of IT clonidine was 57 years (Table 1). Around 17% of patients experienced nociceptive pain, 28% experienced neuropathic pain, and 55% experienced mixed pain. The majority of patients (83%) had ITP catheter tips at T8 and below. There was a wide distribution of cancer types in this study, with the two most prominent being sarcoma and colorectal cancer (Table 2).

For primary outcomes, no significant change in VAS or systemic MME was observed at either follow-up period after starting IT clonidine - though for systemic MME at the second follow-up period, the increase in combined standing plus as-needed MME approached statistical significance (Table 3). Median daily IT bupivacaine and opioids with or without patient-administered boluses significantly rose by the first follow-up; by the second follow-up, only IT opioids were elevated. There was a trend towards a lower prevalence of medication-related side-effects across follow-up periods. With regard to either hypotension, bradycardia, or sedation, three patients endorsed at least one side-effect at the time that clonidine was started; all three denied these side-effects at both follow-ups. Meanwhile, two other patients developed at

Table 1 Patient Demographics

Variable	Value
Total number of patients	18
Mean ± SD age at the start of IT clonidine	56.9 ± 12.3 years
Percent male	44%
Percent with pain types:	
Nociceptive	17%
Neuropathic	28%
Mixed	55%
Percent with catheter tip level at:	
T7 and above	17%
T8 and below	83%

Abbreviations: SD, Standard Deviation; IT, Intrathecal.

Table 2 Cancer Etiology for the Cohort

Cancer Type	N	Cancer Type	N
Myoepithelial	1	Endometrial	1
Neuroendocrine	1	Nerve sheath	1
Sarcoma	3	Cervical	1
Breast	1	Renal	1
Urothelial	1	Squamous cell	1
Lung	2	Colorectal	3
Prostate	1		

Abbreviation: N, Number.

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Table 3 Summary of Study Findings

_	Baseline	Start of Clonidine Dosing	1st Follow-up	2nd Follow-up	1st Follow-up vs Start of Clonidine Difference, p-value	2nd Follow-up vs Start of Clonidine Difference, p-value
Median days passed since baseline assessment	0	15	64	145	-	-
Median (IQR) IT clonidine dose (mcg/day)	-	30.2 (12.5)	41.3 (12.2)	40.7 (37.1)	**+8.8 (17.6), p=0.018**	+3.3 (42.7), p=0.18
Catheter tip T7 and above	-	33.0 (18)	38.0 (13.8)	50.0 (24.4)	-	-
Catheter tip T8 and below	-	30.0 (12.5)	42.5 (13.8)	35.7 (39.8)	-	-
Primary Outcomes						
Median (IQR) VAS pain score	6 (4.8)	5 (2)	6 (4.5)	5 (2)	+0 (3.3), p=0.85	+0 (3), p=0.29
Median (IQR) systemic opioid dose in MME (mg/day), standing only	192 (551)	159 (239)	150 (306)	204 (410)	+0 (160), p=0.58	+0 (324), p=0.59
Median (IQR) systemic opioid dose in MME (mg/day), standing plus all PRNs	259 (691)	165 (555)	204 (395)	576 (1454)	+0 (160), p=0.44	*+354 (1253), p=0.059*
Secondary Outcomes						
Median (IQR) IT bupivacaine dose (mg/day)	9.5 (5.8)	8.0 (6.5)	9.7 (6.9)	8.9 (8.3)	**+1.1 (3.1), p=0.0076**	+1.0 (2.5), p=0.43
Median (IQR) IT opioid dose in MME (mg/day), continuous only	1456 (1608)	1400 (1500)	1515 (3121)	1575 (3700)	**+205 (406), p=0.0024**	*+285 (592), p=0.097*
Median (IQR) IT opioid dose in MME (mg/day), continuous plus all PTMs	3440 (2287)	3050 (3705)	3318 (7399)	3896 (8364)	**+255 (821), p=0.0071**	**+685 (3245), p=0.012**
Prevalence of patient-reported side-effects	50.0%	56%	33%	28%	−23%, p=0.29	*−28%, p=0.13*

Notes: Column headers are bolded and underlined. Statistically significant p-values are in bold. P-values approaching statistical significance (p<0.15) are italicized.
Abbreviations: IQR, Interquartile Range; IT, Intrathecal; NRS, Numeric Rating Scale; MME, Morphine Milligram Equivalents; PRN, as Needed; PTM, Personal Therapy Manager.

least one side-effect transiently at first follow-up, and two endorsed them only at second follow-up. With regard to either numbness, urinary retention, or other symptoms, eight patients endorsed at least one at clonidine start but only three continued to endorse them through the second follow-up. Meanwhile, only one other patient developed new symptoms at both follow-up periods. On post-hoc logistic regression analysis, IT clonidine dosing was the sole significant predictor of medication-related side-effect prevalence – such that higher IT clonidine dosing was associated with a lower likelihood of side-effects (Figure 1). Based on this analysis, a recommended starting dose for IT clonidine between 40–60 mcg/day for cancer pain was chosen to be safe due to its association with a 50–75% lower prevalence of side-effects relative to baseline.

Discussion

While clonidine has been an accepted alternative to LA in TDD systems or as an adjunct to opioid/LA combinations, its safety profile and dosing escalation guidelines for these purposes continue to be unclear in patients with cancer pain.[11,12] Side-effects of IT clonidine include hypotension, bradycardia, and sedation.[16] For single-shot IT spinal anesthetics, clonidine has been shown to be associated with increased hypotension and pressor requirements in a dose-dependent fashion.[17,18] While Filos et al have demonstrated potential pressor effects at IT clonidine doses above 300mcg, this was noted in relatively healthy parturients undergoing C-section.[14] On the contrary, systemic hypotension was seen among patients treated for refractory chronic pain at similar daily IT doses by Hassenbusch et al.[19] All in all, side-effects have unfortunately limited clonidine's use as an adjuvant in TDD.[4,12] In this paper, there was a trend towards a lower prevalence of medication-related side-effects across follow-up periods with the use of IT clonidine. Additionally, when it comes to patients with active oncologic diseases, it is very common for pain scores to increase because of progression of disease. This often dictates greater opioid requirements, thereby producing a higher likelihood of opioid related side-effects. Given the inevitable increase in opioid requirement in patients with active cancer, this study demonstrates that the

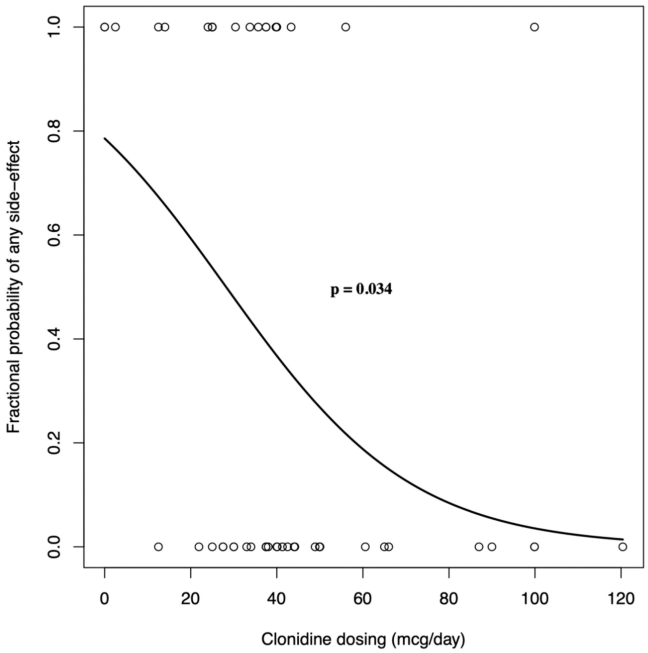

Figure 1 Logistic regression plot of medication-related side-effect probability as a function of intrathecal clonidine dosing. Open circles plot empiric data on which the solid black model curve is based.

use of low-dose IT clonidine as an adjuvant is a safe modality for cancer pain patients that has the potential to reduce medication-related side-effects. Thus, clonidine may be considered sooner as a combination IT medication.

Current IT clonidine starting dosages lie in the 20–100 mcg/day range as recommended by The Polyanalgesic Consensus Conference (PACC),[4] which is a large range. Eisenach et al published one of the first studies utilizing IT clonidine in the chronic pain space - exploring its use at a dose of 150 mcg/day to reduce heat-induced hyperalgesia.[20] In 2003, Ackerman et al performed a retrospective chart review of 15 patients, analyzing the use of IT clonidine as sole therapy or as an adjuvant to opioids for various chronic pain syndromes, with starting doses ranging from 75 mcg/day to as high as 950 mcg/day.[21] Hassenbusch et al also performed a robust dose-titration study of IT clonidine within a similar dose range across 31 patients; however, over 90% of them did not have active cancer pain.[19] With respect to specifically cancer-related pain, Mastenbroek et al performed a retrospective analysis exploring the use of IT clonidine as an addition to morphine and bupivacaine, using starting doses that ranged from 72 to 144 mcg/day.[15] These starting doses are significantly higher than the current PACC recommendations—notably, 33% of patients experienced mild hypotension, which gradually decreased with clonidine dose adjustments. In the present study, we provide data on safe starting doses for IT clonidine to treat active cancer pain that are associated with a significant reduction in side-effects.

Around 75% of patients with cancer require treatment with opioids for pain relief.[22] As tumor burden expands, the increasing opioid requirements that follow can lead to several classic opioid side-effects—sedation, constipation, dizziness, nausea, and vomiting. While it is challenging to limit opioid consumption in the oncologic population, the addition of IT clonidine to pain regimens could help limit side-effects. In the present study with the addition of IT clonidine and despite the progression of disease and/or treatment-related side-effects, the median VAS scores did not increase across follow-up periods. This could also be attributed to the analgesic effects of clonidine requiring smaller increases in the overall IT medication dosage to maintain stable VAS scores. Additionally, there was a trend towards a lower prevalence of side-effects overall with the combination therapy. Furthermore, multivariate logistic regression modeling suggested that higher clonidine dosing was the sole significant predictor of reduced side-effects in our cohort. While chronic pain physicians may not be able to adequately decrease opioid consumption in cancer-related pain, they may consider IT clonidine as a higher-tier, second-line therapy at the starting doses that we recommend for the purposes of maintaining pain relief without compromising hemodynamic stability.

There are several limitations to the present study. Given that this was a retrospective study, there was the lack of control patients for comparison to the patients started on IT clonidine. However, to our knowledge, this is still one of the largest retrospective studies looking specifically at IT clonidine dosing in cancer pain patients. Future prospective, randomized-control studies comparing the addition of IT clonidine to continuation of IT opioids and/or LA would help attribute causality to IT clonidine's role as proposed in this study. Additionally, given that the data were retrospective in nature, MMEs were calculated based on active order information and/or note review in the electronic medical record—unfortunately, if opioid dosing was not adjusted in either of these locations, the true difference would not be picked up. Finally, this is a small-cohort study, and future studies with larger cohorts would be helpful for substantiating our findings.

Conclusion

In cancer-related pain, increases in opioid requirements are often inevitable and may result in medication-related side-effects. Low-dose IT clonidine can be used in this patient population as a first-line adjuvant to local anesthetics and opioids in TDD at initial doses of 40–60 mcg/day. With the addition of IT clonidine, pain relief should be maintained without the progressive development of opioid-related side-effects with increasing doses.

Ethics Approval Statement

This was a Memorial Sloan Kettering Cancer Center Institutional Review Board (MSKCC IRB)-approved (IRB #17-537), single-center, retrospective study of patient records. Patient consent was waived on the grounds that review of records pertaining to prior-received care constituted negligible risk to the patients. Protocols for the safe retrieval, handling, and storage of patient health information were followed in accordance with the Declaration of Helsinki to ensure patient data confidentiality.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

Amitabh Gulati is a consultant for Medtronic, Flowonix, AIS HealthCare, SPR Therapeutics, Nalu Medical, Tremeau Medical, and Neurovasis Inc. Neal Rakesh is a consultant for Neurovasis Inc. No other authors have any relevant financial disclosures.

References

1. Vargas-Schaffer G. Is the WHO analgesic ladder still valid? Twenty-four years of experience. *Can Fam Physician*. 2010;56(6):514–517,e202–5.
2. Meuser T, Pietruck C, Radbruch L, Stute P, Lehmann KA, Grond S. Symptoms during cancer pain treatment following WHO-guidelines: a longitudinal follow-up study of symptom prevalence, severity and etiology. *Pain*. 2001;93(3):247–257. doi:10.1016/S0304-3959(01)00324-4
3. Capozza MA, Triarico S, Mastrangelo S, Attinà G, Maurizi P, Ruggiero A. Narrative review of intrathecal drug delivery (IDD): indications, devices and potential complications. *Ann Transl Med*. 2021;9(2):186. doi:10.21037/atm-20-3814
4. Deer TR, Pope JE, Hayek SM, et al. The polyanalgesic consensus conference (PACC): recommendations on intrathecal drug infusion systems best practices and guidelines. *Neuromodulation*. 2017;20(2):96–132. doi:10.1111/ner.12538
5. Smith TJ, Coyne PJ, Staats PS, et al. An implantable drug delivery system (IDDS) for refractory cancer pain provides sustained pain control, less drug-related toxicity, and possibly better survival compared with comprehensive medical management (CMM). *Ann Oncol*. 2005;16(5):825–833. doi:10.1093/annonc/mdi156

6. Clarke CFM. Neuraxial drug delivery for the management of cancer pain: cost, updates, and society guidelines. *Curr Opin Anaesthesiol*. 2017;30(5):593–597. doi:10.1097/ACO.0000000000000497
7. Portenoy R, Ahmed E, Keilson Y. Cancer pain management: role of adjuvant analgesics (coanalgesics). Up to date. Published December 16, 2022. Available from: https://www.uptodate.com/contents/cancer-pain-management-role-of-adjuvant-analgesics-coanalgesics. Accessed November 11, 2023.
8. Funai Y, Pickering AE, Uta D, et al. Systemic dexmedetomidine augments inhibitory synaptic transmission in the superficial dorsal horn through activation of descending noradrenergic control: an in vivo patch-clamp analysis of analgesic mechanisms. *Pain*. 2014;155(3):617–628. doi:10.1016/j.pain.2013.12.018
9. Gugel A, Ingebretsen EA, Hake HS, Gantz SC. LC-derived excitatory synaptic transmission to dorsal raphe serotonin neurons is inhibited by activation of alpha2-adrenergic receptors. *Neuropsychopharmacology*. 2024;49(6):1014–1023. doi:10.1038/s41386-024-01824-3
10. Coombs DW, Saunders RL, Fratkin JD, Jensen LE, Murphy CA. Continuous intrathecal hydromorphone and clonidine for intractable cancer pain. *J Neurosurg*. 1986;64(6):890–894. doi:10.3171/jns.1986.64.6.0890
11. Newsome S, Frawley BK, Argoff CE. Intrathecal analgesia for refractory cancer pain. *Curr Pain Headache Rep*. 2008;12(4):249–256. doi:10.1007/s11916-008-0043-0
12. De Andres J, Asensio-Samper JM, Fabregat-Cid G. Intrathecal delivery of analgesics. *Methods mol Biol*. 2014;1141:249–278.
13. Bruel BM, Burton AW. Intrathecal therapy for cancer-related pain. *Pain Med*. 2016;17(12):2404–2421. doi:10.1093/pm/pnw060
14. Filos KS, Goudas LC, Patroni O, Polyzou V. Hemodynamic and analgesic profile after intrathecal clonidine in humans. A dose-response study. *Anesthesiology*. 1994;81(3):591–601. (). doi:10.1097/00000542-199409000-00011
15. Mastenbroek TC, Kramp-Hendriks BJ, Kallewaard JW, Vonk JM. Multimodal intrathecal analgesia in refractory cancer pain. *Scand J Pain*. 2017;14(1):39–43. doi:10.1016/j.sjpain.2016.10.002
16. Whizar-Lugo VM, Flores-Carrillo JC, Preciado-Ramirez S. Intrathecal clonidine as spinal anaesthesia adjuvant — is there a magical dose? *Topics Spinal Anaesthesia*. 2014. InTech.
17. Kakunje R, Sethuramachandran A, Parida S, Bidkar PU, Talawar P. Effects of adding low-dose clonidine to intrathecal hyperbaric ropivacaine: a randomized double-blind clinical trial. *Anesth Essays Res*. 2016;10(1):38–44. doi:10.4103/0259-1162.165499
18. Sagiroglu G, Sagiroglu T, Meydan B. The effects of adding various doses of clonidine to ropivacaine in spinal anesthesia. *Eurasian J Med*. 2009;41(3):149–153.
19. Hassenbusch SJ, Gunes S, Wachsman S, Willis KD. Intrathecal clonidine in the treatment of intractable pain: a Phase I/II study. *Pain Med*. 2002;3(2):85–91. doi:10.1046/j.1526-4637.2002.02014.x
20. Eisenach JC, Hood DD, Curry R. Intrathecal, but not intravenous, clonidine reduces experimental thermal or capsaicin-induced pain and hyperalgesia in normal volunteers. *Anesth Analg*. 1998;87(3):591–596. doi:10.1213/00000539-199809000-00018
21. Ackerman LL, Follett KA, Rosenquist RW. Long-term outcomes during treatment of chronic pain with intrathecal clonidine or clonidine/opioid combinations. *J Pain Symptom Manage*. 2003;26(1):668–677. doi:10.1016/S0885-3924(03)00144-1
22. Thapa D, Rastogi V, Ahuja V. Cancer pain management-current status. *J Anaesthesiol Clin Pharmacol*. 2011;27(2):162–168. doi:10.4103/0970-9185.81820