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Research Article

Post Procedural Pain Following Percutaneous Thermal Liver Tumor Ablation under Procedural Sedation and Analgesia: A Single Center Retrospective Cohort Study

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ABSTRACT

Background and Objectives: The incidence of post-procedural pain following percutaneous thermal liver ablation under procedural sedation and analgesia (PSA) is yet largely unknown. Only a few small studies investigated tumor and ablation factors on pain, whereas psychological or PSA factors as possible predictors for pain were not investigated. The primary aim of the current study is to measure the prevalence and severity of post-procedural pain based on maximal NRS. Secondary aim of this study is to identify predictors for post procedural pain post liver ablation under PSA.

Methods: This single center retrospective cohort study was conducted in a tertiary teaching hospital in the Netherlands from November 2018 until May 2023. It involved adult patients (18 years or older) treated with thermal liver ablation under PSA. Prevalence of pain was based on percentage of patients with post-procedural pain (defined as numeric rating scale (NRS) score ≥4).

Results: In total, 170 records of 117 patients were included in the analysis of this study. The prevalence of post- procedural pain after thermal liver ablation was 42.7%. Predictors of post-ablation pain were psychological factors e.g. depression, anxiety disorder or the use of psychopharmacological drugs (β 2.58, 95%CI: 1.44-4.07, p-value<0,001). A background of chronic pain (β 1.23, 95%CI: 0.11-2.36, p-value 0.03), female gender (β 1.09, 95%CI: 0.17-2.01, p-value 0.02) and age (β -0.04 per calendar year, 95%CI: -0.091--0.006, p-value 0.05) were shown to predict acute ablation pain. Tumor location, distinction between primary and secondary tumors and number of tumors did not predict post-ablation pain.

Conclusion: The incidence of post-procedural pain after thermal liver ablation is 42.7%. Predictive factors of post procedural pain after thermal liver ablation under PSA are psychological factors like depression and anxiety as well as the use of psychopharmacological drugs. Tumor characteristics did not predict post-procedural pain after ablation.

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Introduction

Liver cancer is one of the most common types of cancer. In 2020 an estimated 905,700 people were diagnosed with, and 830,200 people died, from liver cancer globally [1]. Hepatic cellular carcinoma (HCC) is the most prevalent type of primary liver cancer with 65% of all cases [2]. Secondary liver cancer is most commonly due to metastasis from the colon cancer, breast cancer or melanoma [2]. The principal treatment for both primary and secondary liver tumors is surgical resection, for which not all patients are suitable [3]. This may be due to the location of the tumor, prior surgery, (severe) co-morbidities, poor hepatic reserve, or advanced cancer stage or the patient's age [3]. In many of these cases, thermal liver ablation can be a good alternative [3, 4].

Thermal ablation in patients with liver tumors is generally performed by an interventional radiologist (IR) under computed tomography-scan or ultrasound guidance and procedural sedation and analgesia (PSA) or general anaesthesia (GA). PSA is monitored by anaesthesia care providers (ACP) and aimed to minimise per- and post-procedural discomfort including pain. In recent years, the number of treatments performed with thermal ablations has risen considerably [5]. The subjective perception of anaesthesia care providers and interventional radiologists is that some patients suffer from severe post-procedural pain after PSA and local infiltration and others do not. The varying and unpredictable occurrence of unacceptable pain during PSA in patients after thermal liver ablation is not completely understood.

Several studies have been conducted to study minimizing pain during PSA in thermal liver ablation patients [3, 6-8]. Based on these studies, an optimal combination of intravenous (i.v.) medication for PSA during thermal ablation induced pain cannot be recommended and remains controversial [6, 7, 9, 10]. Most frequently used and recommended drugs for PSA during thermal ablation are sedatives (e.g. propofol, midazolam) in combination with an opioid (e.g. fentanyl, remifentanil, morphine or piritramide). Optimizing peri- and post-procedural analgesia is of major importance also in view of the prevention of possible complications including the development of acute and/or post-procedural pain [11]. In order to minimize procedural pain during and after PSA, opioids are first choice of treatment.

However, as the use of large doses of opioids is associated with opioid dependence and hyperalgesia, nowadays multimodal PSA based on relatively low concentrations of opioids in combination with IV-medication, is used [8, 11]. Esketamine is an NDMA receptor antagonist, and directly involved in modulating central sensitization, a process known to be pivotal in development and chronification of pain [12]. Esketamine is increasingly used as an adjuvant for postoperative pain control in major surgery where severe postoperative pain is expected to occur and where opioid analgesia has been shown to be inadequate [8, 11, 13-15]. Metamizole is a non-selective NSAID with a strong analgesic effect. The analgesic effect occurs within 30 minutes after intravenous administration and lasts approximately 4 hours [16]. In the Netherlands metamizole has rarely been used since the 1970s because of what was thought to be an unacceptable risk of agranulocytosis [15]. The incidence of metamizole-induced agranulocytosis is controversial, but the risk is likely to be limited with short-term postoperative use in patients with increased risk for stomach or renal problems [17].

The prevalence of post procedural pain after percutaneous tumor ablation under PSA is yet unknown. Therefore, the primary aim of this study was to determine the prevalence and severity of post-procedural pain after percutaneous thermal liver ablation in patients under PSA. Only a few studies on pain post percutaneous thermal liver tumor ablation investigated tumor and ablation factors on pain. However, these studies do not include psychological and PSA factors. Therefore, the secondary aim of this study was to identify predictive factors for development of post procedural pain following transcutaneous tumor ablation under PSA.

Methods

I Study Design & Ethical Approval

This retrospective single-center cohort study was performed at the Maastricht University Medical Centre (MUMC$^+$) in the Netherlands. Ethical approval for this study (METC 2020-2222) was provided by the ethics committee of MUMC$^+$ on 25 August 2020, Maastricht, Netherlands. This study was conducted in compliance with the Declaration of Helsinki and the Good Clinical Practice guidelines.

II Participants

Patients with primary and secondary liver tumors receiving PSA for a percutaneous thermal liver tumor ablation from November 2018 until May 2023 were included in this study. For characteristics of patients included (Table 1). Pre-, per-, and post-procedural anaesthesiologic and radiologic data were required. Exclusion criteria were: age < 18 years, patients who received GA, sedated patients did not receive an ablation.

Table 1: Baseline characteristics of all procedures, NRS 0-3 group and NRS 4-10 group. Values are number (percentages) unless stated otherwise.

		Total (n=170)		NRS 0-3 (n=98)		NRS 4-10 (n=72)	
Sex N (%)	Men	113	66.5	73	74.5	40	55.6
Age - mean (SD)		68	10	69	8	66	11
BMI - mean (SD)		26.9	4.1	26.8	3.9	27.0	4.3
Intoxications	Smoking	36	21.6	18	18.8	18	25.4
	Alcohol	72	43.1	33	33.7	30	41.7
	Drugs	4	2.4	1	1.0	3	4.2
ASA classification	ASA 2	63	37.1	36	36.7	27	37.5

	ASA 3	102	60.0	60	61.2	42	58.3
	ASA 4	5	2.9	2	2.0	3	4.2
History of chronic pain		27	15.9	12	12.2	15	20.8
Psychological factors		17	10.0	3	3.1	14	19.4
Thermal ablation last year		53	31.2	29	29.5	24	33.3
Surgery last year		68	40.0	35	35.7	33	45.8
Prognosis	Curative	153	90.0	90	91.8	63	87.5
Received chemotherapy		54	31.8	32	32.7	22	30.9
Tumor type	Primary	91	53.5	52	53.1	39	54.2
	Secondary	79	46.5	46	46.9	33	45.8
Liver cirrhosis		73	42.9	33	41.8	9	34.6
Number of lesions	1	115	67.6	68	69.4	47	65.3
	2	40	23.5	21	21.4	19	26.4
	>2	15	8.9	9	9.2	6	8.3
Tumor location	Subcapsular	84	49.4	45	45.9	39	54.2
	Deep	85	50.0	52	53.1	33	45.8
Maximum tumor diameter - mean (SD)	Mm	19.8	7.0	19.2	6.7	20.5	7.5
Vascular involvement	No	97	57.4	59	60.2	38	53.5
	<5mm	31	18.3	20	20.4	11	15.5
	Against vessel	41	24.3	19	19.4	22	31.0

BMI: Body Mass Index; ASA-classification: American Society of Anaesthesiologists Physical Status Classification; physiological factors was defined as patients were known to have an episode of depression, anxiety or sleep disorders; SD: Standard Deviation.

III Interventions & Outcome Measures

All patients were treated under moderate to deep sedation. PSA treatment always included an opioid and propofol. The short-acting opioids remifentanil or alfentanil were administered during PSA. Piritramide or morphine in combination with para-acetylaminophenol were administered during PSA to prevent post-procedural pain. Based on the clinician's experience and preference esketamine and/or metamizol was administrated for multimodal treatment. All patients received supplementary local anaesthesia before PRFA started. In some cases loco- regional anaesthesia like spinal or epidural were combined with PSA.

Post-procedural pain (based on the numeric rating scale (NRS)) was assessed at a minimum of 2 time-points : i) upon arrival at the recovery room, ii) at departure of the recovery room. In cases when NRS maximum was not equal to NRS arrival or departure a third time-point during the recovery stay is included for assessment of NRS.

IV Transcutaneous Thermal Liver Tumor Ablation

A pre-ablation ultrasound was performed in all patients. All thermal ablations were microwave ablations and performed transcutaneous with ultrasound or CT-guidance. The procedure was performed by an experienced interventional radiologist (CvdL and SdB). The NeuWave Microwave ablation system (Ethicon; Johnson & Johnson) or the HS Amica generator (HS; Hospital Service) was used for the thermal ablation. The duration of the ablation procedure and the energy level (wattage) were determined by the IR.

V Clinical Assessments

The NRS was questioned by the recovery room staff and documented into the patient data management system (PDMS). The length of stay in the recovery room was automatically recorded in PDMS. During PSA and stay in the recovery room the vital parameters were continuously monitored using the Philips Medical Systems Intellivue MX800 1&2 and automatically stored in PDMS. Administered medication during PSA and recovery stay was entered in real time into PDMS. Anaesthesiology data was collected from PDMS and the pre-operative anaesthesia evaluation form. Risk factors for pain were registered on available data from the electronic patient file and medication overview. Psychological factors were defined as patients who were known to have experienced an episode of depression, anxiety or sleep disorders. Radiological images and reports were assessed using SECTRA IDS7 software (version 23.2.0.2452). Assessment of the images was performed by a trained master medical student and a researcher (K.J. and R.K.) with routine checking by an IR (CvdL). All data required for this study was extracted from the hospital electronic health systems and incorporated in an online database (Castor EDC v2022.5.4.0).

VI Statistical Methods

All analyses were performed using SPSS statistics software version 25.0. A P-value < 0.05 was considered significant. Patient characteristics were described using standard descriptive statistics. The prevalence of pain was tested by using standard descriptive statistics. Linear mixed-effects models were used to accommodate clustering of multiple procedures within patients. Univariable and multivariable models were used to identify baseline characteristics that are associated with the development of having postoperative pain. An NRS difference of 1.4 on the 11-point numeric rating scale was considered clinically relevant [18, 19]. Subsequently, maximum pain intensity (NRS max) was categorised and analysed using univariable and multivariable linear mixed-effects models. The NRS 11-point numeric rating scale was categorised into: acceptable pain (NRS 0-3) and moderate to severe pain (NRS 4-10) [20]. Multivariable models were performed to correct for potential confounding factors i.e. age, sex, history of chronic pain and psychological factors. These were based on expert opinion and previous literature [21-25].

Results

I Patient Characteristics

From November 2018 until May 2023, 170 thermal liver ablations were performed in 117 patients under PSA. Most procedures were performed in male patients (66.5%), the mean age was 68±10 (mean±SD), most frequent ASA classification was 3 (60%) and in most procedures 1 liver lesion was treated (67.6%). The median tumor diameter was 18.8 ±7.0 mm (median±IQR), (range 5-47 mm). Most frequently ablated tumors were HCC (50.5%) and colorectal metastases (46.5%). Patient characteristics at baseline are summarized in (Table 1). The mean length of stay on the recovery room was 103 ± 45 minutes (mean±SD; range 37-281 min).

II NRS Outcomes and Predictive Factors

The prevalence of having a maximal NRS score ≥4.0 was 42.4%. At the recovery the mean maximal NRS score was 3.1±2.8, 95% confidence interval (CI) 2.69 to 3.50. Details of the distribution per NRS score are summarized in (Table 1 of the Supplementary Material). The presence of psychological factors, i.e. depression, anxiety disorder or the use of psychopharmacological drugs (regression coefficient (β) 2.58, 95%CI: 1.44-4.07, p-value<0,001) was associated with higher NRS scores (Table 2). Also, a background of chronic pain (β 1.23, 95%CI: 0.11-2.36, p-value 0.03), female gender (β 1.09, 95%CI: 0.17-2.01, p-value 0.02) and age (β -0.04 per year, 95%CI:-0.091- -0.006, p-value 0.05) resulted in a significant increase of the NRS-score. Location (aβ -0.40, 95%CI: -1.21-0.33), size (aβ 0.02, 95%CI: -0.03-0.08) or type (aβ -0.27, 95%CI: -0.90-0.36) of the tumor did not have a significant effect on the maximum NRS score (Supplementary Material Table 2). Neither the number of lesions (aβ 0.21, 95%CI: -0.24-0.65) ablated nor the duration of anaesthesia (aβ 0.00, 95%CI: -0.09-0.11) or duration of procedure (aβ 0.00, 95%CI: -0.1-0.01) did affect the maximum NRS- score. Esketamine was administered during PSA and tend to reduce the maximum NRS score in 33.5% of the procedures (aβ -0.74, 95%CI: -1.53-0.04, p-value 0.06). Mean dosage of esketamine was 0.17mg/kg SD ± 0.11 (range 0.05-0.55 mg/kg). It is not possible to reliably estimate the effect of metamizole on post-procedural pain as this drug was administered in only 6,5% of the cases.

Table 2: Maximum NRS in univariable linear mixed-effects model.

	β	95% CI	P-value
Gender	1.09	0.17-2.01	0.02
Age*	-0.04	-0.09-0.00	0.05
BMI	0.00	-0.11-0.11	0.99
ASA	-0.06	-0.83-0.72	0.89
Chronic pain	1.23	0.11-2.36	0.03
Psychological factors	2.58	1.44-4.07	<0.001
Smoking	-0.39	-0.98-0.19	0.19
Alcohol	-0.42	-0.85-0.02	0.06
Drugs	-0.83	-1.90-0.24	0.13
Cirrhosis	-0.19	-1.07-0.70	0.68
Chemotherapy**	-0.28	-1.18-0.62	0.55
Surgery**	-0.25	-1.07-0.57	0.55
Thermal ablation**	0.01	-0.83-0.84	0.98
Duration anaesthesia	-0.00	-0.01-0.01	0.98
Duration procedure	0.00	-0.01-0.01	0.75
Maximum tumor diameter	0.02	-0.04-0.07	0.56
Tumor location	-0.30	-1.07-0.47	0.44
Vascular involvement	0.03	-0.45-0.51	0.90
Number of lesions	0.12	-0.36-0.59	0.63

β: Regression Coefficient; CI: Confidence Interval. * per calendar year;** < 1 year prior to treatment.

An average higher NRS score at arrival at the recovery (aβ 0.79, 95%CI:0.69-0.88, p-value <0.001) was shown to be associated with a higher maximum NRS score. Patients with a NRS score ≥4,0 required more analgesics at the recovery (piritramide aOR18.4, 95%CI:7.78-43.45 or morfine aOR 10.64, 95%CI: 2.71-41.74).

Discussion

The incidence of postoperative pain based on maximal NRS score ≥4 was 42.4% after thermal liver ablation. This is slightly lower than reported after upper abdomen surgery [26]. A prevalence of 41% of moderate or severe pain (based on a visual analogue scale (VAS) score of >40) on day 0 after surgery was noted in a group of 1490 surgical inpatients [26]. On day 0, but 1 hour after surgery, when patients were at the recovery room 55% of the patients after intermediate upper abdomen surgery i.e. cholecystectomy and 47% major abdomen surgery i.e. hepatectomy suffered from postoperative pain based on a visual analogue scale (VAS) score of >40 [26]. Hence, our results in patients after thermal liver ablation, a percutaneous minimal invasive procedure, are in the same range as those reported after upper abdomen surgery [26]. Nevertheless liver ablation is characterized by three moments which are known to be painful: skin puncture, liver capsule puncture, as well as the moment of the thermal energy transfer [3]. This then may underlie the fact that this relatively minimal invasive procedure results in an prevalence of postoperative pain similar to that noted after more invasive surgeries like upper abdomen surgery [26].

Previous studies have demonstrated that tumor characteristics such as location, type or size are known risk factors for the occurrence of peri-procedural pain [6, 7, 9, 10, 27]. In our study, tumor characteristics did not predict post-ablation pain. A study by Andreano *et al.* reported an association between the volume of the ablation zone on CT and presence of post procedural pain (NRS ≥ 4.0) [28]. The latter association is also not noted in our study, suggesting a limited effect of tumor type on post procedural pain intensity. One explanation might be that PSA strategies differ between the studies [6, 7, 9, 10]. The depth of sedation varied from light to moderate and moderate to deep. In the groups with light to moderate sedation the patients were able to indicate whether they experienced pain during ablation and if so then the dosage of pain medication was increased. In general patients experience a moment of intense acute pain during ablation which subsequently faded away post-ablation. During moderate to deep sedation, as in our study, patients did not consciously experience pain during ablation. The first notable pain the patients in our study experienced was the pain when they recover and became conscious.

Of those patients which reported NRS ≥ 4 the dosage of analgesics was increased during PSA if there were any signs of discomfort or pain during e.g. face expressions, increasing ventilation rate, tachycardia, hypertension or movement. In all studies reported up till now different combinations of medication were administered [6, 7, 9, 10]. This may vary from midazolam, dexmedetomidine or propofol as sedatives and a range of opioids e.g. pethidine, fentanyl, oxycodone, remifentanil, piritramide or morphine. During PSA there is a limitation on the dosage of opiates due to dose-related complications like respiratory depression sometimes resulting in oxygen desaturation and apnea. Esketamine has been reported not to result in these side-effects and therefore is increasingly used as an adjuvant for postoperative pain [8, 11, 13-15]. Although esketamine does not significantly reduce pain based on the NRS score, it still may prevent patients from reaching clinically relevant levels of NRS score ≥4. In our study it is not possible to reliably estimate the effect of using metamizole due to a small group size. It is thus worth considering a prospective study on the effect of metamizole on post-procedural pain after thermal liver ablation.

This retrospective single-center study has several limitations. Due to the retrospective observational nature of the study we were not able to adjust the analyses for unmeasured potential confounders. Biases might have occurred such as: i) pre-operative pain, ii) psychological factors and iii) sedation strategy. Due to the retrospective design we had to work with the available data from the electronic patient file and medication overview. In 31.8% of the cases there were missing data of pre-procedural NRS scores. The effect of pre-procedural pain on the maximum NRS might therefore be underestimated. Psychological factors were defined as patients who were known to have experienced an episode of depression, anxiety or sleep disorders. The incidence of these psychological factors in our study might be underreported as we used the available data of the electronic patient file. Ideally, the registration is based on prospective data such as validated questionnaires (e.g. Hospital Anxiety and Depression Scale). It has been documented in literature that preoperative high expectations and anxiety of postoperative pain by the patient is also a predictor for postoperative pain [24, 29]. Unfortunately this information was not included into the electronic patient files used for our retrospective study. Finally, it needs to be stressed that sedation practitioners in our study were free in choosing their sedation strategy for the individual patient.

Although the retrospective design of our study might also affected the generalizability of the outcome, the results suggest that predictors for thermal liver ablation are similar to predictors for acute post- operative pain. A follow-up study based on a prospective design is recommended.

Conclusion

First, the incidence of post-procedural pain (NRS score ≥4) after thermal liver ablation is 42.7%. Second, predictive factors of post procedural pain after thermal liver ablation under PSA are psychological factors such as depression and anxiety as well as the use of psychopharmacological drugs, and a background of chronic pain, female gender and age.

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Conflicts of Interest

None.

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