How to make cancer patients have less pain during subcutaneous implantable venous access devices insertion: the effect of buffered lidocaine.

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Abstract

Purpose: Subcutaneous implantable venous access devices are of great importance for the administration of chemotherapy in cancer patients. They are routinely implanted under local anesthesia. However, patients complain of pain during the injection of local anesthesia. Alleviating pain for cancer patients is of high importance. Our aim was to evaluate the effectiveness of sodium bicarbonate-buffered lidocaine with epinephrine on reducing pain and patients' satisfaction during subcutaneous implantable venous access devices insertion.

Methods: A prospective double-blind study was conducted over a period of 6 months (January 2017 to June 2017) in a department of anesthesiology in Tunisia. Cancer patients were randomized to receive either buffered (PH= 7.33) or plane lidocaine (PH= 3.50). Pain and satisfaction were evaluated on a VAS score (0-100 mm).

Results: One hundred twenty patients were enrolled in this study with sixty patients in each group. Mean pain scores during local anesthesia infiltration were 15.7 ± 7.6 mm vs. 46.9 ± 12.3 mm respectively in the study and control group ($p < 0.001$). Mean VAS satisfaction was 95.75 ± 8 mm in the intervention group and 70.2 ± 20.1 mm in the control group ($p < 0.001$).

Conclusion: Adjusting the pH of anesthetic agents could minimize pain during PortACath insertion and improve satisfaction of cancer patients.

Introduction

Multiple venipunctures in order to administer cytotoxic agents and supportive drugs are one of the most uncomfortable and hindering aspects of the treatment of cancer patient. Therefore, subcutaneous implantable venous access devices are of great importance and also safe [1] for those patients. The insertion of long-term central venous access devices (PortACath) is frequently performed under local anesthesia. The field infiltration with local anesthetic is often reported in the literature as being the most painful part of the procedure[2]. Pain related to lidocaine infiltration could be reduced with epinephrine. Several interventions concerning the temperature of the injected solution, the diameter of the needle, the angle and the speed of injection, and the acidity of injected preparations the pH of which is usually equal to 3.5, have been evaluated [3].

The aim of this study was to determine if the addition of a buffering solution to adjust the pH of lidocaine with epinephrine into the physiologic range would reduce pain during injection within patients scheduled for Porta-Cath (PAC) insertion.

Materials And Methods

This prospective, randomized, controlled, double-blinded study (NCT03628430, Date of retrospective registration: August 9, 2018) was done in the Anesthesia and Resuscitation Department of Farhat Hached

University Hospital of Sousse over a 6 months period (1st January 2017 to 30th June 2017). Ethical approval was obtained from the the research Ethics Board of Farhat Hached University Hospital. Before entering this study, a written informed consent was obtained from each patient by the investigators. Adult patients who were scheduled for PAC placement under local anesthesia in order to administer chemotherapy were included.

Patients whose pain characteristics and intensity can change were excluded from the study: pregnant women, patients with a known allergy to study drugs or using opioids or benzodiazepine, patients having a neuropathy, patients with a history of thoracic or cervico-facial radiotherapy and those with severe respiratory or cardiovascular compromise.

Patients were randomized in a double blind manner (using computer-generated allocation numbers sealed in brown envelopes) to receive one of two local anesthetic solutions. The A group was the pH adjusted group. They received 5 mL of 4.2% sodium bicarbonate added to 10 mL of 2% lidocaine with epinephrine 0.005mg/ml (Lidocaine adrenaline; Aguettant, France). The C group was the control group and they received 5 mL of 0.9% NaCl added to 10 mL of 2% lidocaine with epinephrine 0.005mg/ml (Lidocaine adrenaline; Aguettant, France) .

A member of the anesthesia team freshly prepared the local anesthetic solutions and balanced them at room temperature 30 minutes prior to the procedure. The anesthetist in charge of the patient was not aware of the prepared solution. have been measured using A pH-meter (PH-meter/millivoltmeter 3510 JENWAY) allow us to measure the pH values of the final formulations at the beginning of the study. In the control group, pH was 3.5 and in the study group it was 7.33.

Heart rate, blood pressure, oxyhemoglobin saturation, and respiratory rate were monitored as soon as the patient arrived at the operating room. Conditions of surgical asepsis were controlled. A prerequisite depilation, a cleaning of the area, rinsing, drying, an application of an antiseptic and then the setting of sterile drapes widely extending beyond the catheterization area were performed to prepare the insertion area of the PAC. No The patients did not receive any preoperative sedation or any type of topical anesthetic or pain reducing technique before the injection of the anesthetic mixture.

An ultrasound allow the operator to confirm suitability of the target subclavian vein. A syringe containing one of the randomly assigned local anesthetics was given to the operator. Thanks to ultrasound guidance, 3 mL of the local anesthetic solution through a 25 gauge needle were deliberately injected directly superficial to the subclavian vein and lasted 10 seconds with the same angle of injection with regard to the skin. Afterwards, the needle was repositioned to inject 12mL to infiltrate the skin and deep tissue of the targeted area of the anterior chest wall. A 7 Fr catheter via a non-tunneled approach was received by the patient. Each patient was given instructions on rating pain and satisfaction via a standardized 100 mm horizontal linear visual analog scale (VAS). A score of 0 represented no pain (very satisfied) and 100 represented the worst possible pain (not satisfied).

The primary outcome of this study was pain assessed on VAS with five procedural steps: 1) the infiltration of local anesthetic, 2) the cannulation of the central vein, 3) the incision of the skin, 4) the dissection the deep tissue and the pocket formation, and 5) the closure of the skin. Sensory block onset time using pinprick test and patients' satisfaction were secondary outcomes.

The required sample size was calculated hoping for a decrease of 30 mm of the VAS score during the injection of the local anesthetic after alkalinization, with a power ($1-\beta$) of 90%, a non-directional risk α of 5%, and assuming a standard deviation of 42, the size of the sample per group was estimated at 42. The sample size was increased to 60 patients per group in order to prevent the possible missing data or violation of the protocol.

We collected data on customized data collection sheets and analyzed by a statistical software (IBM® Statistical Package for Social Science (SPSS), New York, USA version 21.0). A p value of 0.05 was considered statistically significant. Quantitative variables were expressed in average and standard deviations and compared with the Student's t-test. Qualitative variables were expressed in numbers and percentages and compared using Pearson Chi-2 test.

Results

During our study period, 186 patients were scheduled for PAC placement. One hundred thirty seven of eligible patients were approached for participation, of whom 17 (12.4%) declined. One hundred twenty patients were enrolled, all completing the study protocol. Neither complications nor major event requiring stopping of the protocol were noted within the two groups (Figure 1).

There were no significant differences between the two randomized groups of patients in terms of age, gender, or cancer type (Table 1). When tested by pinprick the onset times of sensory block was significantly less important in the group A, 3.25 ± 1.3 min vs 5.5 ± 1.3 with $p < 0.001$.

Table 1
Comparison of sociodemographic characteristics and neoplastic pathology origin in both groups.

	Group A (n=60)	Group C (n=60)	p
Age (mean ± SD)	51.5 ± 12.7	50.2 ± 12.6	0.51
Gender	22 (36.7)	27 (45)	0.35
Man (%)	38 (63.3)	33 (55)	
Woman (%)			
Cancer localization	24 (40)	28 (46.7)	0.53
Breast (%)	1 (1.6)	4 (6.7)	
Ovary (%)	19 (31.7)	17 (28.3)	
Colorectal (%)	4 (6.7)	3 (5)	
Gastric (%)	12 (20)	8 (13.3)	
Other (%)			

There was a statistically significant difference in pain scores among groups during different procedural steps (Table 2).

Table 2
Comparison of perioperative pain score and patients' satisfaction between the two groups.

	Group A (n=60)	Group C (n=60)	p
Local anesthetic infiltration	15.7±7.6	46.9±12.3	0.0001
Central vein cannulation	8.5±7	14.4±9.7	0.0001
Skin incision	4.9±6.6	10.8±7.6	0.0001
Deep tissue dissection and pocket formation	12.8±9.9	35±20.4	0.0001
Skin closure	3.6±7.7	7.4±8.1	0.008
Satisfaction	95.75±8	70.2±20.1	0.0001

The mean of the VAS satisfaction was of 83±19.94 mm for the general population. It was of 95.75±8 mm in the intervention group and of 70.2±20.1 mm in the control group (p<0.001).

Discussion

According to our study, lidocaine with epinephrine alkalization proved its effectiveness in the reduction of perioperative pain and in the improvement of patients' satisfaction. Anesthesia quality was better with

a shorter onset time.

These data have been supported by several studies published in the literature. It seems that pain linked to the infiltration of LA is due to its acidity. Therefore, lidocaine alkalinization was able to have such analgesic effect [4–17].

An improvement of anesthesia quality and patients' satisfaction has also been reported [7, 9, 18–20, 20–22]. In Yiannakopoulos's study [23] assessing patients' satisfaction during the carpal tunnel decompression under local anesthesia by lidocaine, 55% of participants in the control group (non-buffered) declared that they would refuse to undergo again the same anesthetic technique vs. only 18% patients in the intervention group.

However, other studies did not find a benefit for lidocaine alkalinization [24–28]. These results need to be interpreted with caution. Actually, most of these studies have been conducted in patients with an infection or an acute inflammation, which interferes with the local acido-basic characteristics and makes alkalinization rather random. Changes in the characteristics and the intensity of pain during the inflammation are also possible, thus making the evaluation of the perioperative pain more difficult. It is worth noting that other studies have been conducted in children scheduled for central venous catheterization. It is a non-representative sample of the general population in particular, to its specificities in terms of perception and evaluation of the perioperative pain [29].

Although the same administration protocol was used by Culp et al [30] (needle size, speed of injection, angle with regard to the skin, and ultrasound guidance), they did not find that alkalization of lidocaine decreased pain-related injection of local anesthetic. This may be due to the use of non-equivalent local anesthetic concentrations.

On the basis of Henderson-Hasselbach equation ($\log [\text{basis}] / [\text{acid}] = \text{pH} - \text{pKa}$), it is clear that an anesthesia with a low pH will tend to exist predominantly in the state of loaded cations with less available free base to pass across the nerve membrane, therefore the block onset time will be much slower. The anesthetic solute alkalinization allows decreasing this time [31].

Mayrl et al. compared the corneal permeability of non-buffered lidocaine to buffered lidocaine [32]. They showed that anesthetic solutions buffered at pH 7 had an increased penetration rate which causes a shorter setting delay and a more extended action time with a reduction of the local irritation and lacrimation.

A double blind randomized study about 44 volunteers showed that a buffered solution of 1% lidocaine provided an anesthetic effect longer than the non-buffered one [33].

Lidocaine topical anaesthetic seems to have antibacterial effects on various micro-organisms. Such effect is not compromised by alkalinization [34].

A retrospective review of all patients with Mohs micrographic surgery for basal cell carcinoma was conducted between October 2002 and January 2009 to assess the association between local anesthesia (0.5% of buffered lidocaine and 1: 200 000 epinephrine) and the postoperative complications, including infection or necrosis.

Out of 63 patients presenting for a surgical intervention (59 fingers and 4 toes), no case of digital ischemia or infection was reported [35].

Conclusion

Lidocaine is commonly used in the medical care to facilitate a variety of invasive procedures. Injected subcutaneously, it can cause enough severe pain often described as a burning sensation. It is suggested that such pain is due to the increase of hydrogen ions in the local tissue environment due to the acidity of lidocaine.

Our results have shown that lidocaine alkalization can reduce the intensity of pain in cancer patients at the time of the injection, improve anesthesia quality and the postoperative analgesia thus leading to a better patients' satisfaction. This inexpensive and harmless intervention is to be considered in the current practice especially since its pharmacological impacts are minor.

Declarations

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• Conflicts of interest/Competing interests:

The authors have no relevant financial or non-financial interests to disclose

• Availability of data and material:

This manuscript adhered to institutional policies regarding data collection and research. Code availability: not applicable.

• Authors' contributions:

All authors contributed to the study conception and design, material preparation, data collection and analysis and writing of the manuscript. All authors read and approved the final manuscript.

• Ethics approval:

This study was performed in accordance with the Declaration of Helsinki. Ethical approval was obtained from the Research Ethics Board of Farhat Hached University Hospital (Sousse, Tunisia).

• Consent to participate:

Written informed consent was obtained from all participants before entering this study.

• Consent for publication:

not applicable

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Figures

Figure 1

Study flow diagram