Introduction

Postoperative Pain is considered an undesirable and expected effect of surgery; hence, an effective postoperative analgesia regimen is considered indisputable. Tramadol is an effective analgesic for the relief of moderate to severe postoperative pain [1]. It has an original action profile on both weak opioid agonist on μ receptors, and as a reuptake inhibitor of norepinephrine and serotonin [2]. Tramadol is a prodrug that requires bioactivation to obtain O-desmethyltramadol which has the analgesic effects of tramadol. This bioactivation is done through the hepatic enzyme (CYP2D6) of the cytochrome P450 family which has genetic polymorphisms. In the Caucasian population, 10% of people do not have CYP2D6 activity. Thus, tramadol will have no analgesic effect on them [3-5]. However, the pharmacokinetic and pharmacodynamic profiling of drugs ensures their rational use, providing a precise description of the dose-concentration-
effect-toxicity relationships [6]. In our setting, few studies have been conducted on the clinical and pharmacological monitoring of analgesic drugs. Hence, we carried out this study on the therapeutic follow-up of tramadol in patients admitted in the postoperative period, in the intensive care unit (ICU) of the Yaoundé Gyneco-obstetrics and Pediatric Hospital (HGOPY).

**Patients and Methods**
This was a prospective cohort study conducted over a 3-month period in the ICU of HGOPY, as well as in two laboratories. Sampling was consecutive and non-exhaustive. We included patients who underwent surgeries of moderate to severe pain, without altered consciousness, with no notion prior administration of drugs metabolised by CYP450 enzymes and with no hepatic or renal failure.

**Clinical evaluation**
Sociodemographic data, the type of surgery and the technique of anesthesia were studied. Tramadol was administered over 15 minutes at a dose of 2mg/kg intravenously diluted in 100ml of infusion every 6h. Pain assessment with the Visual Analogue Scale. (VAS) was done at admission into the ICU and then at the 20thmin, 3rdh, 6thh, 12thh & 24thh respectively, following tramadol administration. Clinical parameters and side effects were recorded. We collected 3-5ml of blood sample in EDTA tubes at the 3rd & 6th hour after administration of tramadol.

**Laboratory analysis**
The collected blood was centrifuged for 20 minutes at 4000rpm to extract the plasma in search for O-desmethyltramadol.

**Plasma pre-treatment: liquid-liquid extraction**
In 500µg of plasma, we added a drop of 0.1mol/L NaOH. The mixture was vortexed for one minute. We added 1ml of extracted solvent which was made of ethylacetate + cyclohexane in the ratio of 1:4. The mixture was vortexed a second time for one minute and then centrifuged at 400rpm for 15 minutes. The organic phase obtained was then transferred to vials to be introduced into the autosampler.

**Preparation of the HPLC**
We used an HPLC-UV chain with RP C18 tubes with 5µm particles, 250x4.6mm PHENOMENEX® brand. The eluent or mobile phase was acetonitrile/phosphate buffer (KH2PO4 0.01M solution) in proportions: 30/70 which was then mixed with triethylamine at a concentration of 0.1% TEA. The pH of this mobile phase was adjusted to 3. The injection volume was 10µl with a flow rate of 1ml/min and a separation time of 7 minutes. The detection was set at 218nm UV at room temperature.

The data obtained was analyzed on the software SPSS version 20 and EPI INFO version 3.5.4. The statistical study was descriptive with the study of proportions and means.

**Results**

**Socio-demographic and clinical data**
We recruited 30 patients with a mean age of 32.8±10.26 years. ASA 1 patients (60%) were the most represented. Caesarean section was the most performed surgical procedure (80%), followed by laparotomies (ectopic pregnancy and pelvic infection) and gynecological oncological surgeries. Spinal anesthesia (RA) was the most commonly performed anesthesia technique (54%) followed by general anesthesia with orotracheal intubation (AG + IOT) in 43% of patients.

**The modalities of administration of tramadol**
Tramadol was averagely administered at a dose of 100mg/kg intravenously every 6 hours. It was always used in balanced analgesia with level 1 analgesics, mainly paracetamol (70%).

**Assessment of pain before tramadol administration**
When evaluating the pain intensity of patients prior to tramadol administration, the mean VAS was 5.933±1.257. The intensity of the pain was higher in patients who underwent exploratory laparotomy (6.3/10) (Figure 1). When the vital signs were taken, the respiratory rate was the only slightly elevated parameter varying up to 25 cycles/min (Table 1).

**Assessment of pain following tramadol administration**
After administration of tramadol, a reduction in pain intensity was observed as early as the 20th minute. This reduction was 2 points or around 3/10 for all patients at the 3rdh compared to the

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*Figure 1: Evaluation of pain intensity before tramadol administration with respect to the type of surgery.*

| Type of surgery          | Pain intensity (VAS) |
|--------------------------|----------------------|
| Cesarean                 | 6.6                  |
| Chronic gynecological    | 6.4                  |
| Laparotomy               | 5.933                |
| Exploratory laparotomy   | 6.333                |

*Table 1: Assessment of clinical parameters prior to tramadol administration.*

| Parameters | Mean   | Ecart-type | Minimum | Maximum |
|------------|--------|------------|---------|---------|
| SBP (mmHg) | 124.4667 | 15.2694 | 100 | 165 |
| DBP (mmHg) | 75.3333 | 12.455 | 50 | 100 |
| HR (beats/min) | 85.1 | 15.4124 | 52 | 120 |
| RR (cycles/min) | 21.7667 | 14.2074 | 14 | 35 |

SBP: Systolic blood pressure; DBP: Diastolic blood pressure; RR: Respiratory rate; HR: Heart rate.
intensity of the pain before the administration of tramadol. From the 24thh, the VAS was about 1/10 (Figure 2).

During the evaluation of the parameters, a decrease in systolic blood pressure of 20mmHg was observed at the 3rdh & 6thh respectively for patients who underwent an exploratory laparotomy and a carcinological surgery. Concomitantly, a regression of 10mmHg was recorded for diastolic blood pressure. We observed a regression of 2 to 3 respiratory cycles per minute for all patients and 10 beats per minute reduction in pulse rate.

The main adverse effects of tramadol concerned mainly the gastrointestinal tract (30% of nausea cases and 13.30% of vomiting cases), followed by cholinergic effects (dryness of mouth in 16.7% of cases) and neurological effects especially vertigo (3.30%).

**Plasma determination of O-desmethyltramadol**

When we performed the plasma determination of 13 patients. We found the active metabolite of tramadol: O-desmethyltramadol (M1). Overall, there was good agreement between clinical and laboratory data (Figure 3). However:

Four patients had a slower metabolism (Table 2)
Three patients had a faster metabolism (Table 3)

#### Table 2: Relationship of VAS and biological assay in patients with slow metabolism.

| Patient 1 | Patient 2 | Patient 3 | Patient 4 |
|-----------|-----------|-----------|-----------|
| VAS at the 3rdh | 7 | 5 | 6 | 4 |
| VAS at the 6thh | 5 | 3 | 5 | 3 |
| M1 Concentration at the 3rdh (µg/ml) | 3.28 | 12.53 | 13.53 | 15.53 |
| M1 Concentration at the 6thh (µg/ml) | 3.15 | 11.82 | 35.11 | 24.43 |

#### Table 3: Relationship between VAS and biological assay in patients with rapid metabolism.

| Patient 1 | Patient 2 | Patient 3 |
|-----------|-----------|-----------|
| VAS at the 3rdh | 4 | 6 | 5 |
| VAS at the 6thh | 1 | 5 | 5 |
| M1 Concentration at the 3rdh (µg/ml) | 14.53 | 16.53 | 17.53 |
| M1 Concentration at the 6thh (µg/ml) | 3.53 | 2.46 | 1.96 |

#### Discussion

The average age of our patients was 32.8±10.26 years, which corresponds to the generally young age of the Cameroonian and African population. Caesarean sections were most performed surgical procedures explained by the fact that the study setting is a hospital specialized only in the management of mother and child pathologies.
Paracetamol was the main analgesic used in combination with tramadol. In effect, the pain after caesarean section, exploratory laparotomy or cancer surgery is classified as strong in the first 48 hours according to the WHO [7]. As such, it seems logical to propose tramadol as part of a balanced intravenous analgesic regimen [2]. In addition, with respect to the combination of tramadol + paracetamol, a meta-analysis of randomized clinical trials conducted on postoperative dental, orthopedic and gynecological pain showed the analgesic superiority of tramadol-paracetamol compared to the other analgesic effect tramadol or paracetamol [8].

The mean VAS before tramadol administration was 5.93±1.257/10, explained by the fact that preemptive analgesia was started during the intraoperative period. A significant reduction in pain intensity was observed for all patients at the 3rdh compared to the intensity of the pain before administration of tramadol. This reduction is more than 50% at the 24thh compared to the baseline VAS before administration of tramadol. This threshold significance was proposed in 2003. These data seem to agree with the pharmacokinetic data with respect to the time of action, the half-life and the plasma peak of tramadol [6].

With regards to the side effects of tramadol, we mainly found the gastrointestinal (nausea, vomiting), cholinergic effects (dryness of mouth) and vertigo. This finding concurs with that of the literature [6]. Of the 30 patients enrolled, 13 had postoperative biological monitoring of the concentration of tramadol and O-desmethy tramadol or M1 at the 3rd & 6thh after administration of tramadol. Overall, there was good agreement between clinical and biological parameters. An African study in Ethiopia [9] was previously performed without the biological assay of tramadol. Our results are in line with this study as far as patient satisfaction is concerned.

We wanted to go further than this by testing the hypothesis that patient satisfaction using VAS may be consistent to some extent with the biology of tramadol and O-desmethy tramadol. We found that those who metabolize slowly have better satisfaction with the analgesic effect. On the other hand, in those who seemed to metabolize rapidly, the VAS decreased but remained generally at levels of moderate pain values. This is in good correspondence with the literature on the subject [10].

We will have been able to have more samples tested, to measure more specific pharmacokinetic parameters such as the area under the curve, the plasma clearance and the half-life, for example [11]. Nevertheless, our results allow us to know the metabolism profiles (CYP 2D6) of our patients indirectly. In addition, tramadol + paracetamol combination could compensate for the effect of tramadol on VAS values, if tramadol shows low plasma concentrations at the same time.

Conclusion
In our cohort made up of a young population, we obtained a good analgesic efficacy of tramadol at the biologically and clinically; highlighting the metabolic profile of our patients.

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