

Intrauterine Infusion Of Levobupivacaine Vs. Placebo Associated Towound Infiltration In Elective Caesarean Delivery

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Abstract

Randomized, double blind study, 60 Caesarian sections: all were given the same premedication, spinal anaesthesia and post-operative analgesia. Case group: pre-incisional infiltration with 10 ml Levobupivacaine 2.5 mg/ ml and the same quantities on the lower uterine segment; control group: same pre-incisional infiltration and 10 ml of physiological solution at uterine level. Assessments: NIPB, blood saturation, HR, uterine contractility, duration of operation, bleeding and complications, V.N.S. at 3, 6, 12 hrs., rescue analgesics, complications and customer satisfaction. Statistical analysis: variance analysis and Bonferroni test. Minor V.N.S. data and rescue analgesic data in the cases group, but not statistically significant; no differences in bleeding and uterine contractility. The abundant uterine vascolarisation disfavours contact between local anaesthetic and nerve ending. Possible evolution: combination of local anaesthetics with adrenalin. Extending the study to a larger sample is to be assessed. It might also be useful to combine the local anaesthetic with anti-inflammatory drugs.

INTRODUCTION

The choice of the anaesthetic technique to perform a caesarean section depends on several factors, among which the degree of emergency, the presence of certain pathologies in the maternal case history (i.e. coagulopathies, neuropathies, bronchopneumopathies, etc.), the degree of accuracy in following preoperative fasting, as well as the patient's choice. Whatever the case, this choice must guarantee the highest safety level to the mother, the fetus and the newborn, in order to prevent neonatal depression and to provide the gynaecologist with the best preoperative condition.

Nowadays, it can be argued that neither general nor regional anaesthesia is risky for the newborn – providing that they are correctly performed. Even though neurobehavioural changes occur more frequently after general anaesthesia, their effects don't seem to last long. Recently, it has been argued that regional anaesthesia is safer for the fetus, on the basis of retrospective analysis of case histories. However, as far as mothers are concerned, it is proved that general anaesthesia is riskier in terms of morbidity and mortality: the latter is associated to hypoxia due to failed intubation, together with gastric regurgitation and massive aspiration (Mendelson's Syndrome)[1].

Regional anaesthesia, other than allowing the mother to be awake during the childbirth, grants a better placental flow, a better carbohydrate and acid-base homeostasis, a lower catecholamine release and a better postoperative condition (lower PONV rates, less sleepiness, milder pain etc.), which allows an earlier nutrition and breast-feeding.

In order to improve postoperative pain management, it is now a well-established surgical procedure the performance of a peri-incisional infiltration of local anaesthetics, so that it can be reduced the quantity of analgesics injected, which, when taken in large doses, may lead to a toxic effect. Local anaesthetics, thanks to their diffusion characteristics in tissues, block the afferent nerve endings wherein it has been injected; these are the peripheral endings of the nociceptors, whose cell bodies are located in the dorsal root ganglia. They are the least organized peripheral receptors and, as already stated, unlike other more specialized structures, they are made up of free nerve endings lacking peripheral structures capable of transducing and filtering information contained in peripheral stimuli.

Local anaesthetics act on the neuronal membrane, conditioning the possibility of increasing the sodium permeability, thus being responsible for the rising phase of action potentials, for the slowdown in impulse propagation

progress, and for the lessening and, if necessary, the block of stimuli conduction[₂].

The onset time, duration and intensity of a nerve block depend on several factors, especially on the nerve fibre diameter: the larger the diameter, the higher the demand for analgesic drugs. The fibres involved in peripheral injections are afferent sensory roots, large from 0.4 to 1.2 µm in diameter, that is the smallest measure found in biophysical classification of these tissues: this means that, in order to perform a peripheral nerve-conduction block, just a small amount of local anaesthetics is needed. The promptness of a nerve block onset time depends also on the distance between the nerve and the site wherein drugs have been injected: in the case of peripheral injections, it is very short, so that the onset time, duration and peak plasma concentration are at their best.

According to this principle, in literature it is often suggested to perform injections of such drugs directly into peripheral organs, membranes and body cavities; for instance, in several studies, local anaesthetics were administered by intraperitoneal, intravesical and intraprostatic injections.

Our study's purpose is firstly to assess whether administering local anaesthetics in the lower uterine segment to patients undergoing caesarean sections under subarachnoid anaesthesia may have an additional effect to that of the well-established wound infiltration procedure, in terms of postoperative pain management; secondly, whether this procedure may affect haemorrhage and perioperative complications.

In the skin tissue, nerves spread towards adipocytes of hypodermis as sympathetic adrenergic fibres; at the dermis level they reach papillae and then partly go through epidermis. Their structure is organized in plexuses, that are thicker at papillae level, where most fibres are amyelinic: it can be discerned a deep nervous plexus – innervating dermis and epidermis – and a superficial one – innervating dermis – which are differently anastomosed among themselves. Nerve fibres contain a large proportion of sensory fibres transmitting tactile, thermal and pain stimuli. Sensory fibres innervate skin and its appendages in two different ways, namely as free or encapsulated nerve endings. The latter are a bundle of nerve cells enclosed in a sheath of connective tissue.

Uterine innervation comes from the uterovaginal plexus of the inferior hypogastric plexus which is in its turn part of the

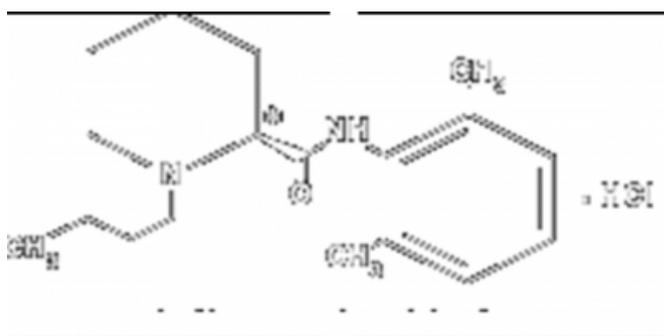
thoracolumbar sympathetic nervous system. Parasympathetic fibres terminating in such plexus travel in sacral nerves; through such nerves and the thoracic spinal nerves from 10 to 12 and the lumbar spinal nerve 1 run also the sensory fibres, which arise from the uterus and converge towards the spinal cord[₃].

In uterovaginal plexus there is a great ganglion, the so-called cervical ganglion, which is connected to two little urinary bladder ganglia which are close to ureter. Fibres forming vagina, bladder and ureter innervation arise from the uterovaginal plexus, while fibres composing uterus converge in a plexus located in the surface of it, from which thin fibres arise, go through the myometrium, spread over musculature and the blood vessel wall, and end in the endometrium.

The anaesthetic drug chosen for a peripheral block is levobupivacaine (Chirocaine™ –): it is S-isomer of bupivacaine, an amino-amide local anaesthetic widely used in regional anaesthesia, in postoperative analgesia and in treatment of acute and chronic pain[₄]. This drug produces sensory and motor nerve conduction block, acting on sodium channels of the cell membrane – sensitive to electric stimulus – but also on potassium and calcium channels. Moreover, it is remarkable for a rapid onset time and a long duration.

Figure 1

Chemical structure of levobupivacaine



In vitro and in vivo pharmacodynamic studies show that levobupivacaine has the same potency as bupivacaine, though the former is less likely to cause cardio- and neurotoxicity. A study carried out on sheep, comparing two different infusive therapies, showed that the convulsive dose of levobupivacaine was remarkably higher than that of bupivacaine. Tests on healthy volunteers showed that levobupivacaine has a minor negative inotropic effect and ECG results showed that it also causes a less prolonged QT interval than bupivacaine. Moreover, in tests using

levobupivacaine, minor EEG changes occurred – meaning a CNS depression.

MATERIALS AND METHODS

We recruited 60 women into the study and they provided us with a previous written consent: their most important anthropometric parameters are showed in Table I.

- All patients underwent an elective caesarean section (see Table II for indications, parity and mean duration) under subarachnoid anaesthesia.
- Criteria according to which patients were not recruited into the study are the following:
- Coagulation alterations (hypocoagulability);
- Anamnesis of hypersensitive reactions to local anaesthetics;
- Severe deformation of spinal column, osteoporosis;
- Local infection wherein the injection should be performed;
- Patient's refusal

All patients underwent the same anaesthetic technique, namely the insertion of a 16-gauge catheter to gain a peripheral venous access straight after their arrival at the operating block. Then, an antibiotic prophylaxis was immediately performed, by intravenous administration of 1.2 g amoxicillin + clavulanic acid in 100 ml of physiological salt solution (in case of patients with hypersensitivity to this drug, 200 mg of ciprofloxacin), together with a fluid load (lactate Ringer's solution 500-1000 ml), as a prevention from induced hypotension following subarachnoid anaesthesia.

After such treatment, the patient was carried to the operating theatre, where NIBP, ECG, and Sa O₂ were monitored. Then, subarachnoid anaesthesia was performed in sitting position at L₂₋₃, L₃₋₄, or L₄₋₅ spaces, with intrathecal injection of 1% hyperbaric bupivacaine (12-15 mg) and morphine 80 µg, using a pencil-point needle (Pencan B Braun, 88-103 mm, 25 or 27 G) inserted parallelly to dura mater fibres, in order to prevent headache following spinal puncture.

The patient was then placed in supine decubitus and the operating bed was put in Trendelenburg position for a while (1-2 mins), in order to achieve a greater block height,

providing an optimal anaesthesia up until T₅ - T₆ level. The achievement of a correct block height was checked by testing thermal and pain sensitivity. Meanwhile, a 15 to 20 cm wedge was placed beneath the patient's right gluteal muscles, in order to relieve aortocaval compression of the fetoplacental unit and the associated hypotension occurred upon assuming the supine position.

Afterward, the bed was placed back to a neutral position, the block height was tested again, and the operation was performed as follows: skin disinfection, incision until the fascia, diastasis recti, lower uterine segment section, amniotic fluid observation and extraction of the fetus. Then, manual placenta removal, cleaning of the abdominal cavity, control of hemostasis and layered closure with intradermal suture were carried out.

The case group, before the incision, was treated with a periincisional infiltration of levobupivacaine 10 ml, chlorhydrate 2.5 mg/ml (10 ml syringe, 20 G x 1 ½' needle) and the same amount was administered in the lower uterine segment before abdominal closure; the control group was treated with the same periincisional infiltration, whereas a physiological salt solution 10 ml was administered in the uterus.

At the end of the operation, patients received analgesics – ketorolac 30 mg and tramadol 100 mg – gastroprotectives – ranitidine chlorhydrate 50 mg – and antiemetics – ondansetron 4 mg; all this drugs were dissolved in 100 ml IV of physiological salt solution.

During the operation the following parameters were monitored (Table III):

- NIBP, Hr, Sa O₂;
- Total haemorrhaging;
- Uterine contractility;
- Obstetric and gynaecological complications;
- Anaesthetic complications.

During the first 24 hours following the operation, it was observed a recovery of gait and complications occurred were examined (see Table V), focusing mainly on:

- Haemorrhaging;

- PONV;
- Diuresis;
- Bowel movement;
- Hypersensitive reactions.

Postoperative pain (Table IV) – either at rest or on movement i.e. coughing – was observed after 3, 6 and 12 hours following the operation, according to a Verbal Numerical Scale: patients assessed pain intensity rating it on a scale from 1 to 10.

Medical staff administered rescue analgesics in case of pain-related complaints by the new mother (upon demand). In case of postoperative V.N.S. being between 4 and 6, ketorolac 30 mg IV was administered (maximum daily dose 90 mg); whereas, in case of higher V.N.S. it was prescribed an IV infusion of tramadol 100 mg (obviously excluding patients with known sensitivities or allergies to this pharmacological category), with a maximum daily dose of 300 mg. Meanwhile, it was observed the total quantity of analgesics demanded by patients during the first 24 hours following the operation and, at the time of patient’s discharge, it was assessed her satisfaction towards the treatment received on a scale from 0 to 10 (Table VI).

Verbal Numerical Scale: patients assess pain intensity on a scale from 1 to 10:

- no pain
- mild pain
- moderate pain
- severe pain
- worst possible pain

RESULTS

Table I summarizes patients’ anthropometric parameters.

Figure 2

Table 1: Patient’s Characteristics

CONTROL GROUP			CASE GROUP	
RANGE	AVERAGE		RANGE	AVERAGE
18 – 41	34,53	AGE (yrs)	33,13	16 – 40
55-100	66,80	WEIGHT (kg)	64,93	60 – 105
18 – 28	21,97	BMI	21,47	14 – 27

28	I			I	28
1	II			II	2
1	III	ASA		III	0
0	IV			IV	0
Tot. 30					Tot. 30

The two groups under study match in age, weight and mean BMI: the mean age varies from 33.1 to 34.5 years, and weight varies between 64.9 and 66.8 kg. Similarly, they were equivalent in terms of anaesthesiological risk assessment according to A.S.A. scale: the majority of both groups were classified as A.S.A I grade, namely the class of patients not suffering from life-threatening diseases. No patients classified as A.S.A IV were treated, whereas in the control group there was a case of A.S.A III.

Table II lists the major clinical indications that supported surgeons’ choice of performing an elective caesarean section.

Figure 3

Table 2: Indications

CONTROL GROUP			CASE GROUP	
PREVIOUS SECTIO	11		PREVIOUS SECTIO	11
PSYCHOLOGICAL AIMS	6		PSYCHOLOGICAL AIMS	7
CTG ALTERATIONS	5		CTG ALTERATIONS	4
TRANSV.FETAL POSIT.	2		PODALIC FETAL POSIT.	4
PODALIC FETAL POSIT.	2		SEVERE PIH	1
PLAC. PRAEVIA	2		TWINNING DELIVERY	1
METRORRHAGIA	1		MATERNAL EPILEPSY	1
MECCANIC DISTOCY	1		MECCANIC DISTOCY	1
Tot.	30		Tot.	30

RANGE	AVERAGE		AVERAGE	RANGE
35 – 90	48,67	DURATION	38,8	30 – 65

19	I			I	19
11	II			II	10
0	III	PARITY		III	1
0	IV			IV	0

In both groups, the larger category is that of patients having had a prior caesarean delivery – 11 cases out of 30, that is 37% ; then, it is listed the category of patients showing an unusual psychological attitude contraindicating a natural childbirth – 6 c-sections out of 30 (20%) in the group of control and 7 out of 30 (23.3%) in the case group. Further indications, which are numerically less represented, came

out from tests on both groups: cardiotocographic abnormalities, abnormal fetal position, placenta praevia, multiple births, maternal epilepsy, severe gestational hypertension, metrorrhagia before labour and cervical dystocia.

The average duration of operations was 51.67 minutes – with a range from 30’ to 90’ – in the group where intrauterine injection of levobupivacaine wasn’t performed, whereas it was 36.8 minutes in the second group, with values ranging from 30’ to 65’.

Table II shows also data about parity of patients: the two groups were almost identical, both showing 19 cases of primiparas and all the rest of biparas; the only exception was a para 3, who belonged to the group receiving intrauterine injection of local anaesthetics.

Table II shows also data about the average duration – and range of minutes – of operations: in the control group the average value is 49’, while in the case group it is around 39’.

Table III lists all intraoperative parameters that are important in contrasting the two groups: regarding intraoperative haemorrhage, the control group shows an average of 415 ml every operation, ranging from 90 to 755 ml; whereas, the case group shows an average of 385 ml – with a range of 105-605 ml. Even though these data showed different averages, their difference didn’t result to be statistically significant when subject to T-test with Bonferroni correction.

Figure 4

Table 3

INTRAOPERATIVE PARAMETERS				
CONTROLS			CASES	
RANGE	AVERAGE		AVERAGE	RANGE
90 – 755	415	BLEEDING(ml)	385	105 – 605

UTERINE CONTRACTILITY		
10	EXCELLENT	13
16	GOOD	14
4	SUFFICIENT	3
0	NOT SUFFICIENT	0
Tot. 30		Tot. 30

COMPLICATIONS		
CONTROLS		CASES
0	HYPERTENSION	0
5	HYPOTENSION	6
0	ARRYTHMIAS	0
0	CONSCIOUSNESS DISEASES	0
0	IPERSENSIBILITY REACTIONS	0
5	PSYCOMOTOR AGITATION	5
7	NAUSEA	8
5	VOMITING	3
0	OTHERS	1

Regarding uterine contractility, that was intraoperatively stimulated by intravenous infusion of oxytocin 20 units, no significant differences between the two populations arose: the control group showed an excellent contractility in 10 cases, good in 16 and sufficient in 4; similarly, the case group showed an excellent contractility in 13 cases, good in 14 and sufficient in 3. Cases of insufficient contractility never occurred.

The most frequent intraoperative complication, in the control group, turned out to be nausea (7 cases): apart from being often a parapsychological symptom arising during pregnancy, it is intensified by low blood pressure due to subarachnoid anaesthesia, together with the aortocaval compression syndrome caused by the gravid uterus. Other frequent complications were hypotension, vomiting and psychomotor agitation with tremors (5 cases each).

Similarly, the case group showed the following intraoperative complications: 8 instances of nausea, 6 of hypotension and 3 of vomiting. In one case, severe preoperative agitation, probably associated to severe bradycardia and low blood pressure due to aortocaval compression, caused a syncope, that didn’t last long and was treated with intravenous infusion of atropine 1 mg, ephedrine 12.5 mg followed by hydration with succinyl gelatine 500 ml.

All the complications occurred in both groups were not

severe and were effectively treated: nausea and vomiting with a dose ranging from 4 to 8 mg of ondansetron, drop in blood pressure with ephedrine (maximum of 25 mg) and psychomotor agitation with benzodiazepines, obviously after having extracted the fetus.

Table IV summarizes average V.N.S. values of patients analysed, after 3, 6 and 12 hours from the operation.

Figure 5

Table 4

PAIN				
		3 h.	6 h.	12 h.
CONTROLS	VNS REST	1.72 ± 2.21	3.07 ± 2.76	3.63 ± 2.45
	MOVEMENT	3.23 ± 3.25	4.47 ± 3.21	5.63 ± 2.41
CASES	VNS REST	2.02 ± 2.15	3.25 ± 2.95	4.75 ± 2.54
	MOVEMENT	2.95 ± 3.05	4.17 ± 2.56	4.83 ± 2.45

Data were collected with the patient either at rest or on movement (i.e. while coughing). In both groups and in both analysis – either at rest or on movement – average data tend to slightly increase with the passing of hours. Regarding the control group, the average V.N.S. at rest was 1.72 (3 hrs), 3.07 (6 hrs), 3.63 (12 hrs); the same trend was observed in the case group, with 2.02 after 3 hours, 3.25 after 6 hours and up until 3.75 after 12 hours. Data describing pain due to movement show higher average values, but an identical trend.

These data were submitted to a statistical analysis (analysis of variance and T-test with Bonferroni correction) and proved that the difference in averages wasn't significant.

Table V lists postoperative complications.

Figure 6

Table 5

POSTOPERATIVE COMPLICATIONS		
CONTROLS		CASES
1	HAEMORRHAGE	0
6	NAUSEA	7
3	VOMITING	4
0	DIURESIS CONTRACTION	0
0	INTESTINAL PERISTALSIS PROBLEMS	0
0	IPERSENSIBILITY REACTINS	0
0	OTHERS	0

In the control group, as it was found about intraoperative complications, the most frequent one resulted to be nausea (6 cases). Secondly, 3 patients suffered from prolonged vomiting. Finally, there was one case of severe postoperative haemorrhage. Similarly, patients treated with an intrauterine

injection of levobupivacaine complained of the same most frequent symptoms (nausea and vomiting). Severe problems never occurred, such as anuria, bowel movement, or hypersensitive reactions.

Table VI summarizes the total amount of analgesics administered (ketorolac and tramadol) during the first day of admission.

Figure 7

Table 6

RESCUE ANALGESICS		
CONTROLS		CASES
57	KETOROLAC 30 mg	53
24	TRAMADOL 100 mg	20
7,40	CUSTOMER SATISFACTION (0-10)	7,55

The control group was subject to a total of 57 injections of ketorolac 30 mg and 24 of tramadol 100 mg, whereas patients that were subject to an intrauterine injection of levobupivacaine were treated with a total of 53 injections of ketorolac 30 mg and 19 of tramadol 100 mg. No patients complained of such an intense pain that opioids had to be administered as analgesic supplements.

Patients' satisfaction about the operation and postoperative pain management was sufficient, with an average value of 7.40 in the control group and 7.55 in the case group (on a scale from 0 to 10).

DISCUSSION

In literature, there are many studies about periincisional and visceral infiltration techniques of local anaesthetics aimed at relieving postoperative pain: Grossmann et al.[5] indicate an infiltration of the scalp with lidocaine and bupivacaine after craniotomy; Macpherson A.[6] studies buccal mucosa infiltrations of lidocaine after complicated surgery in pediatric dentistry under general anaesthesia; Lavand'homme P.M. et al.[7] indicate a continuous wound infiltration with diclofenac after elective c-section, whereas during knee prosthesis, Andersen L.J. et al.[8] perform an infiltration with ropivacaine, ketorolac and adrenaline.

Similarly, Petterson et al.[9] perform a wound infiltration with ropivacaine after inguinal hernia repair, Glosch Y.K. et al.[10] during ophthalmic surgery, Gurbet A. et al.[11] during lumbar laminectomy, and Rica MA et al.[12] during breast surgery. As already mentioned while naming just a few studies in literature, wound infiltration is widely performed

in many different surgical areas. However, local anaesthetics may be administered in different parenchyma, deeper than the cutis. This topic as well has been widely studied: for instance, Nunez A.I.^[13] performs uterine curettage with infiltration of local anaesthetics in the parametrium, Ahmed B.H. et al.^[14] perform peritoneal infiltration after laparoscopic cholecystectomy, and Nikandish R. et al.^[15] perform an infiltration in the peritonsillar space after tonsillectomy.

Regarding patients' anthropometric parameters, as already mentioned, the two groups matched in terms of age, weight, mean BMI, and A.S.A. scale. It is not the purpose of this study to discuss indications to c-section, and the difference between the two groups in mean duration of operation (48.67' in the control group, 38.8' in the case group) is only due to a different surgical team.

Regarding indications to the performance of a c-section, it never occurred the existence of comorbidity in terms of blood and coagulation pathologies, which may alter findings obtained about perioperative haemorrhage: even though without any statistical evidence, haemorrhage occurred to a lesser degree in patients treated with periincisional and intrauterine infiltration of chirocaine. Moreover, in this group, cases of severe postoperative haemorrhage never occurred (just one case in the control group). The possible injection of local anaesthetics together with adrenaline may give rise to future assessment of any significant difference in perioperative haemorrhage. Besides, the treatment of a control group with a placebo injection either in the wound or in the uterus could be contrasted to the combined technique.

The case and the control group are equivalent also in terms of uterine contractility which doesn't show any insufficiency caused by the administered drugs: with the conventional support of oxytocin, the degree of uterine contractility is the same as it is observed in c-section deliveries performed without any peripheral infiltration, which confirms that levobupivacaine – at least in the dose we administered – doesn't have any influence upon it.

Intraoperative complications occurred in cases under study don't show any difference between the two groups and are the same as those occurred in c-section deliveries performed without peripheral infiltrations: also our study showed that hypotension, nausea and vomiting are the most frequent complications, that are caused by physiologic changes due to pregnancy. Therefore, the infiltration of levobupivacaine

can't be their cause.

Observing the Table about postoperative pain, it can be argued that there isn't any statistically significant difference between the case and the control group, despite lower mean measures obtained in the group that underwent wound and uterine infiltrations. It might be interesting to widen the population study in order to observe whether this difference can get a statistical significance. Also the greater quantity of analgesics administered to the control group – even though it is not statistically significant – may support the hypothesis that a wider population study could give rise to changes from a statistical point of view.

The rich uterine blood supply associated with sympathicoplegia due to subarachnoid anaesthesia may in some way obstacle the contact between local anaesthetics and nerve endings, causing a quick absorption of the drug and so stopping the analgesic effect.

The idea of a further study arises out of this hypothesis: local anaesthetics will be administered together with a correct dose of adrenaline, in order to lower uterine blood supply and improve the peripheral nerve endings block.

Besides, since pain is caused not only by a stimulus of nerve fibres but also by inflammatory mediators having algogenic effects, it might be interesting to associate local anaesthetics to anti-inflammatory drugs and to assess their effectiveness in terms of V.N.S. reduction.

Thus, the study confirms how a single-shot peripheral nerve block with local anaesthetics in a given dose is considered as a safe technique free from specific complications (i.e. structural alterations of muscular fibre due to a continuous administration). This technique is a valid support to the performance of intravenous analgesia, within the current framework where multimodal analgesia is very efficient and widespread. In addition, effective pain management is a fundamental component in determining patients' satisfaction; since patients are assuming increasing importance within the health care system, it is vital to provide high quality services in order to achieve an effective clinical and business management.

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