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Original article

Comparison of two different approaches to hypotension following spinal anaesthesia for Caesarean delivery: effects on neonatal and maternal wellbeing

Michele Zasa[1,2], Eleonora Conci[1], Alessandro Marchignoli[1], Rita Pini[1], Lorenzo Passeri[1], Guido Fanelli[1], Andrea Cornini[1]

[1] Department of Anaesthesiology, Intensive Care and Pain Medicine - University Hospital of Parma, Parma, Italy; [2] Clinica Mobile nel Mondo, World Motorbike Championship (MotoGP & WSBK) Medical Division, Parma, Italy

Summary. *Background:* Maternal hypotension during spinal anaesthesia for Caesarean delivery is a common event, with potential detrimental consequences. We led a prospective, randomized study to compare the effects of two strategies on neonatal and maternal wellbeing. *Methods:* Parturients scheduled for elective Caesarean section in spinal anaesthesia were preoperatively studied with a supine stress test. Those with a positive test were enrolled in the study and received a solution of 0.5% hyperbaric bupivacaine 12.5 mg and 0.02% morphine 200 μg intrathecally. Patients received a 37.5 mg/h preventive intravenous (IV) infusion of ephedrine (Pharmacologic Group), or a 15° left lateral tilt (Non-Pharmacologic Group). In Pharmacolgic Group hypotension was treated for 20% drops in systolic blood pressure; in Non-Pharmacolgic Group only severe hypotension – defined as a 40% drop in systolic blood pressure – was treated. *Results:* Thirty-six patients were studied. Study groups were statistically similar in terms of demographic variables and intraoperative times. No statistical differences were found in terms of umbilical arterial blood base excess [-1.4 (-3.7 to -0.3) mEq/l Pharmacologic Group vs. -1.7 (-2.7 to -1.0) mEq/l Non-Pharmacologic Group; p=0.815] and other umbilical blood gas values. Apgar scores were statistically similar between study groups. Treatment for hypotension was required by 13 (72.2%) patients in Pharmacologic Group and 9 (50%) patients in Non-Pharmacologic Group (p=0.171). No differences were found at the analysis of serial changes in vital signs. *Conclusions:* Both studied strategies guaranteed a comparable safe outcome in terms of maternal and neonatal wellbeing. (www.actabiomedica.it)

Key words: anesthesia, spinal, complication, hypotension, Cesarean section, neonatal outcome; ephedrine

Introduction

Maternal hypotension during spinal anaesthesia for Caesarean delivery is a common event, which can have consequences on the mother such as nausea and vomiting, and faintness (1, 2). Moreover, maternal hypotension can cause an impairment of uterine blood flow (3) which may result in foetal hypoxia, acidosis and neonatal depression (4).

Both pharmacological and non-pharmacological approaches have been proposed to manage – that is to say to prevent and treat – this medical condition. Although none has proven a clear superiority over the others, uterine displacement and the use of vasopressors seem to be the most effective and reliable strategies. However, it has been argued that an excessive use of vasopressors may be too aggressive if considering the true incidence of major complications from

hypotension (5). Furthermore, it may expose both the mother and the newborn to risks that outweigh benefits, such as hypertension, reflex bradycardia and placenta vasoconstriction.

Therefore, we developed a pragmatic study to compare two different clinical approaches: to administer preventive vasopressors and treat minor hypotensive episodes with further rescue vasopressor; or rather to displace the uterus and to accept a sort of permissive hypotension, thus limiting the administration of rescue vasopressor to major hypotensive episodes.

The main endpoint of this prospective, randomized study was to compare the umbilical arterial blood base excess produced by the studied strategies. Other neonatal and maternal wellbeing indicators were studied as secondary endpoints. This trial was registered at Clinical Trial.gov with registration number NCT00991627.

Materials and methods

With Local Ethical Committee approval, patients undergoing spinal anaesthesia for elective Caesarean section underwent a supine stress test (SST); those with a positive result were prospectively studied.

The test was performed in order to identify patients at increased risk for hypotension during Caesarean section under spinal anaesthesia. In fact, spinal block is more likely to impair the haemodynamic balance of patients with a positive SST (6).

Enrolment criteria also included: ASA physical status class I or II, age ≥ 18 years, indication for and parturient's agreement to spinal anaesthesia with local anaesthetics and morphine; surgery scheduled for within 4 days of physiological term. Exclusion criteria were: pregnancy-induced hypertension, indication to anticipated or emergency Caesarean section, cardiovascular disease, diabetes, fetal complications, and contraindication to spinal anesthesia and/or any study drugs.

Patients were instructed to cease oral intake 12 hours before surgery, but they were allowed to drink moderate amounts of clear fluids until 6 hours before surgery. Before moving to the operating room patients underwent SST; those with a positive result were asked for written informed consent and enrolled in the study. A positive SST consisted of an increase of greater than 10 beats/min in maternal heart rate or leg flexion movements during a period of 5 min in the supine position (6).

On arrival to the operating room, standard monitoring was applied including electrocardiography (Lead II), heart rate, pulse oximetry and noninvasive arterial blood pressure. An 18G intravenous cannula was then inserted into the forearm and a fast intravenous (IV) infusion of 10 ml/kg of Ringer's lactate solution was completed in approximately 15 minutes. At the end of the infusion patients were placed in the sitting position and spinal anaesthesia was performed at the L_2-L_3 or L_3-L_4 interspace, with a 25G Whitacre needle inserted through an introducer needle (Beckton-Dickinson Italia, Buccinasco, Milan, Italy). A solution of 2.5 ml hyperbaric 0.5% bupivacaine (12.5 mg total; Molteni SpA, Scandicci, Florence, Italy) and 1 ml 0.02% morphine (200μg total; Bupiforan, Baxter Italia, Rome, Italy) was injected intrathecally. Parturients were then placed in the supine position and a 25ml/min IV infusion of Ringer's lactate was started.

Using a random sequence (Random Sequence Generator, available at http://random.org/sequences/; last accessed 15/09/2009), patients were assigned to one of the following study groups:

- Pharmacologic Group: patients were administered preventive IV 0.025 mg/ml ephedrine through the basal Ringer's lactate infusion (37.5 mg/h infusion rate). In this group hypotension was treated for values of systolic blood pressure (SBP) 20% below the baseline.
- Non-Pharmacologic Group: an obstetric wedge was placed under patients' right hip, resulting in a 15° left lateral tilt measured with a goniometer. In this group only severe hypotension - defined as a 40% drop in SBP - was treated.

Hypotension was treated with IV boluses of ephedrine 6.25 mg, repeated if needed, until SBP was restored to the baseline levels. In both groups severe bradycardia was defined as a 50% drop in heart rate and treated with IV atropine 0.5 mg; if it didn't solve within 30 seconds, further IV atropine 0.5 mg was given every 30 seconds until resolution. After delivery, patients received oxytocin 5 IU by slow IV injection.

The following data were collected: demographic variables, incidence of hypotension and bradycardia, use of rescue medications, incidence of nausea and/or vomiting, intraoperative times (time from anaesthesia to delivery, from anaesthesia to skin incision, and from skin incision to delivery). After delivery, Apgar scores were assessed at 1 and 5 minutes by the attending pediatrician, and arterial and venous blood samples were taken from a double-clamped segment of umbilical cord for blood gas analysis. Vital signs were recorded in the supine position before spinal anaesthesia (baseline values); reassessed immediately after spinal anaesthesia, at 2-min intervals until delivery, and then 1 minute and 2 minutes after delivery.

Data were collected by an investigator not involved in intraoperative care.

Statistical Analysis

The null hypothesis of the study was that no difference exists between the umbilical arterial blood base excesses produced by the studied strategies; the alternative hypothesis was that umbilical arterial blood base excess is modified when the uterus is displaced with a left lateral tilt and the use of ephedrine is limited to major hypotensive episodes.

To calculate the required sample size, we took into account results of previous studies. We considered a standard deviation (SD) of 3 mEq/l (7), deeming that a 3 mEq/l difference between groups with regards to umbilical arterial blood base excess would be clinically important (8). Accepting a two-tailed α-error of 5% and a β-error of 20%, 17 patients per group were required. However, taking into account a 5% potential dropout rate, 18 patients per group were enrolled. Statistical analysis was performed using the software SPSS 17.0 (SPSS Inc, Chicago, IL).

Data distribution of continuous variables was analyzed using visual inspection of quantile-quantile distribution plots and the Kolmogorov–Smirnov test. Depending on data distribution, comparisons between continuous variables were made using Student *t*-test (normal distribution), or Mann–Whitney *U*-test (non-normal distribution). Pearson's Chi-square tests or Fisher's exact tests were used for categorical data, while related samples were analyzed using the Wilcoxon signed-rank test. Continuous variables are presented as median values (1st-3rd quartile); categorical variables are presented as count (% within group). Serial changes in arterial blood pressure and heart rate were analyzed using the Mann–Whitney *U*-test, with Bonferroni correction for eight comparisons.

A p-value ≤ 0.05, after appropriate corrections for multiple comparisons, was considered significant.

In order to avoid any bias, the investigator in charge of performing statistical analysis was not aware of group assignment, neither took part in data collection nor in intraoperative care.

Results

Thirty-six patients were enrolled in the study. Figure 1 is a flowchart of patient enrollment according to CONSORT recommendations. No significant differences were found in terms of patients' characteristics and intraoperative times (Table 1).

Umbilical arterial blood base excess was not significantly different between study groups [-1.4 (-3.7 to -0.33) mEq/l Pharmacologic Group vs. -1.7 (-2.7 to -1.0) mEq/l Non-Pharmacologic Group; p=0.815];

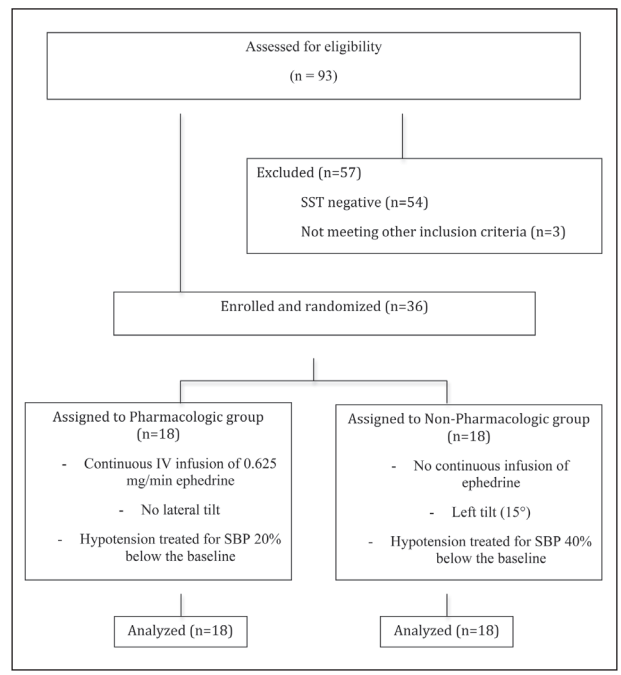

Figure 1. CONSORT-style diagram for the study

Table 1. Parturients' characteristics and intraoperative times. Data presented as median values (1st-3rd quartile) or count (% within group)

	Pharmacologic Group (n=18)	Non-Pharmacologic Group (n=18)	*p*-value
Age (y)	35 (28 - 38)	34.5 (33 - 38)	0.628
Height (cm)	160 (160 - 169)	163 (160 - 167)	0.782
Weight before pregnancy (kg)	58.5 (53 - 68.5)	61 (52.75 - 74.25)	0.673
Weight at the end of pregnancy (kg)	72 (66.75 - 83.5)	74.5 (66.75 - 84.5)	0.719
Pregnancy weight increase (kg)	13 (9.5 - 16)	12 (10 - 14.25)	0.613
ASA Physical Status:			
- Class I	14 (77.8%)	12 (72.2%)	0.457
- Class II	4 (22.2%)	6 (33.3%)	
Fetal Presentation:			
- Head-down position	15 (83.3%)	13 (72.2%)	0.691
- Breech position	3 (16.7%)	5 (27.8%)	
Gestational age (weeks)	38 (38 – 39)	38 (38-39)	0.546
Neonatal weight (kg)	3.3 (2.8 - 3.4)	3.2 (3 - 3.4)	0.767
Time (min):			
- from anaesthesia to skin incision	4 (3 – 4)	4 (3 - 5)	0.339
- from skin incision to delivery	5 (3 – 7)	5 (4 - 7)	0.815
- from anaesthesia to delivery	9 (7 - 12)	10 (8 - 11)	0.542

ASA: American Society of Anaesthesiologists; BMI: Body Mass Index

Table 2. Umbilical cord blood gas values. Data presented as median values (1st-3rd quartile)

	Pharmacologic Group (n=18)	Non-Pharmacologic Group (n=18)	*p*-value
UA Base Excess (mEq/l)	-1.4 (-3.7 to -0.3)	-1.7 (-2.7 to -1.0)	0.815
UA pH	7.30 (7.25 - 7.38)	7.31 (7.28 - 7.34)	0.650
UA Bicarbonate (mEq/l)	24.7 (23.9 - 27.3)	25.0 (24.0 - 26.2)	0.938
UA pCO_2 (mmHg)	53.3 (43.4 - 62.4)	51.4 (43.6 - 55.9)	0.767
UV Base Excess (mEq/l)	-1.8 (-3.1 to -0.9)	-1.8 (-3.0 to -0.4)	0.791
UV pH	7.35 (7.30 - 7.38)	7.36 (7.34 - 7.38)	0.563
UV Bicarbonate (mEq/l)	24.1 (22.9 - 25.3)	24 (23.5 - 24.9)	0.938
UV pCO_2 (mmHg)	44.2 (42.0 - 51.8)	43.4 (41.5 - 45.8)	0.443

UA: umbilical artery; UV: umbilical vein

other umbilical blood gas values were similar between groups, as well (Table 2). Apgar scores at 1 minute [9 (9-9) Pharmacologic Group vs. 9 (9-9) Non-Pharmacologic Group; p=0.563] and at 5 minutes [9 (9-9) Pharmacologic Group vs. 9 (9-9) in Non-Pharmacologic Group; p=0.988] were statistically comparable. Furthermore, only 1 (6%) newborn in Pharmacologic Group had a 1-min Apgar score <7, compared to no one in Non-Pharmacologic Group (p=1.000). In both groups, no Apgar scores <7 were revealed.

Incidence of nausea and/or vomiting was not statistically different between groups [12 (66.7%) patients in Pharmacologic Group vs. 16 (88.9%) patients in Non-Pharmacologic Group; p=0.228].

Following groups' different rules, treatment for hypotension was provided to 13 (72.2%) patients in Pharmacologic Group and 9 (50%) patients in Non-Pharmacologic Group (p=0.171). The amount of rescue ephedrine given to patients treated for hypotension was not statistically different between groups [12.5 (7.8 – 17.2) mg in Pharmacologic Group vs. 6.3 (6.3-18.8) mg in Non-Pharmacologic Group; p=0.310].

Bradycardia occurred to 3 (16.7%) patients in Pharmacologic Group and 1 (5.6%) patient in Non-

Pharmacologic Group (p=0.603). The amount of rescue atropine given to patients treated for bradycardia was not statistically different between groups [0.5 (0.5 - 0.8) mg in Pharmacologic Group vs. 0.5 (0.5 - 0.5) mg in Non-Pharmacologic Group; p=1.000].

No statistical differences were found at the analysis of serial changes in systolic and diastolic blood pressure (Figure 2; all *p*-values ≥ 0.207 and 0.029, respectively), and heart rate (Figure 3; all *p*-values ≥ 0.306).

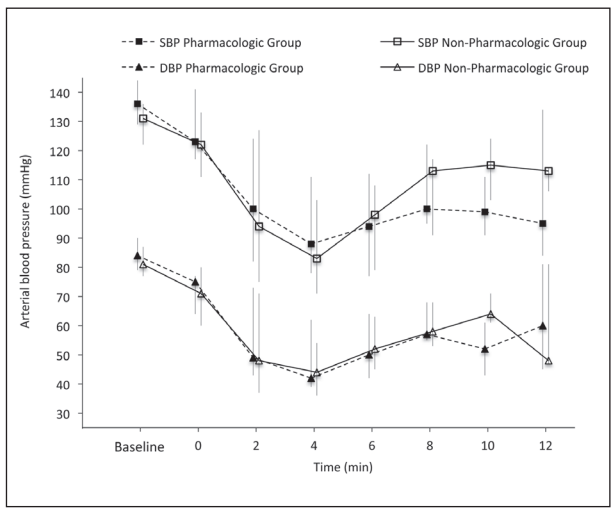

Figure 2. Serial changes in systolic and diastolic blood pressure before delivery. Data are presented as median (1st-3rd quartile). All *p*-values ≥ 0.207 (SBP) and 0.029 (DBP)
SBP: systolic blood pressure; DBP: diastolic blood pressure

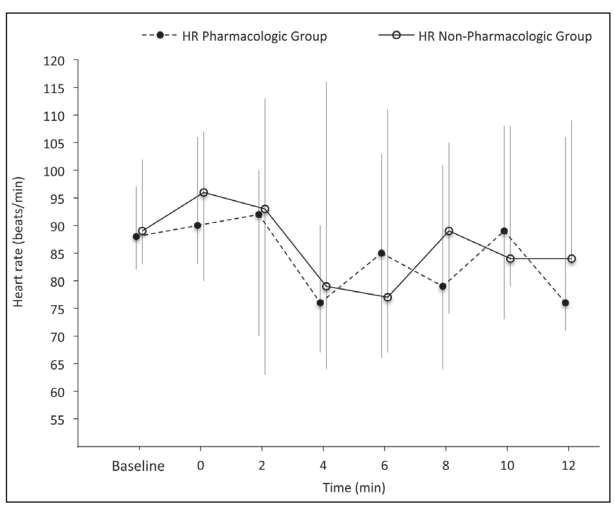

Figure 3. Serial changes in heart rate before delivery. Data are presented as median (1st-3rd quartile). All *p*- values ≥ 0.306
HR: heart rat

Post-delivery serial changes of vital signs were not statistically different between groups, as well (all *p*-values ≥ 0.097).

At the analysis for related samples, overall post-delivery values of vital signs were not statistically different from last pre-delivery measures (all *p*-values ≥ 0.0549); however, a trend towards an increase in post-delivery values of vital signs was noticed, especially in terms of heart rate and diastolic blood pressure.

Discussion

Hypotension following spinal anaesthesia for Caesarean delivery is common in clinical practice and, according to Macarthur, the identification of an infallible technique to prevent spinal anaesthesia-induced hypotension may represent the 'Holy Grail' of obstetric anaesthesia (9). From a physiological point of view, a reduction in venous return due to the compression of the inferior vena cava by the gravid uterus results in a fragile haemodynamic balance in parturients (10). Spinal block produces a decrease in maternal vascular resistances leading to vasodilation, venous pooling of blood in the lower limbs and diminished venous return; thus, spinal anaesthesia precipitates the haemodynamic balance and causes hypotension. Accordingly, parturients affected by aortocaval compression (11) are more likely to experience hypotension during spinal anaesthesia for Caesarean section. Far from providing a definitive solution, our prospective study compared the effects of two common approaches to the problem.

Preventive measures have been extensively discussed and several solutions have been proposed (12). Methods employed to reduce the incidence of maternal hypotension can be distinguished in pharmacological and non-pharmacological ones; pharmacological approaches involve the use of vasopressors (1, 13-17) while non-pharmacological strategies include intravenous fluid prehydratation (18), mechanical systems to improve venous return (19) and left uterine displacement (10). Although the debate on the best strategy is still ongoing, uterine displacement and the use of vasopressors seem to be the most effective and reliable ones at the moment. Therefore, we routinely employ them

in our clinical practice, and we consistently adopted them in the present study.

Left uterine displacement of the gravid uterus seems to be a logical approach to manage hypotension as it relieves aortocaval compression by dislodging the gravid uterus (10). On the other hand, many studies proved that the use of vasopressors to manage maternal hypotension following spinal anaesthesia is effective, as well (13-15, 20-24). Nonetheless, Beilin argued that vasopressors may have detrimental effects on maternal and foetal wellbeing; consequently, risks linked to vasopressors extensive use may outweight benefits (5). In response to this criticism, Ngan Kee and colleagues argued that hypotension has not to be underestimated since scientific data suggest that it may be associated with neonatal acidosis and low Apgar scores (5, 25). According to present results, both pharmacological and non-pharmacological strategies are safe and guarantee a comparable outcome in terms of maternal and neonatal wellbeing.

We evaluated foetal outcome through umbilical cord blood gas values, considering the arterial base excess as the most reliable indicator of foetal wellness. According to Thorp et al. (26) umbilical artery blood reflects foetal status, while venous umbilical blood reflects maternal acid-base status and placental function. At the analysis of blood gas values, previous studies (27) showed that base excess is more reliable than pH values to predict foetal outcome, since base excess does not change significantly with respiratory acidosis and shows linear correlation to the degree of metabolic acidosis. Consequently, umbilical artery base excess is the most direct measure of foetal wellbeing. Depending on factors such as the definition of normality and the study population, normal ranges for umbilical cord blood gas values may vary. However, both arterial and venous values reported in our study are in line with those reported by previous studies dealing with the issue of maternal hypotension following spinal anaesthesia for Caesarean section (1, 13, 14, 17, 18, 9, 20-24). Neonatal wellbeing was also assessed through Apgar scores: both 1-min and 5-min scores did not differ between groups. Moreover, Apgar values confirmed that both approaches are reliable in terms of newborn outcome.

The incidence of nausea and/or vomiting, number of bradycardic episodes and amount of given rescue atropine needed were evaluated to assess maternal wellbeing, along with intraoperative serial changes in vital signs and amount of administered rescue ephedrine. All maternal parameters were statistically similar between groups; thus, the two approaches were not different in terms of maternal wellness.

This study has several limitations. A first limitation is represented by the design of the study, comparing two approaches involving several different conditions. However, we led a pragmatic study whose aim was to compare two different approaches commonly adopted by anaesthetists, at least at our institution.

Since they consider maternal hypotension detrimental at any level, some anaesthetists routinely use a preventive infusion of vasopressors and administer further rescue vasopressor for mild hypotensive episodes. Lateral tilt is not routinely adopted among them, since they only rely on the pharmacological reversal of the vasoplegia caused by the spinal block; this position is supported by a recent metanalysis showing that there is limited evidence to support the use of lateral tilt (28).

On the contrary, others consider placental vasoconstriction vasopressor-associated far more dangerous, so that they only use vasopressors to treat major hypotensive episodes. Among them the lateral tilt is often adopted as an easy harmless measure to reduce compression on venous return.

Pragmatic designs have several limitations; however, they allow to compare treatments adopted in everyday practice. Therefore, we believe that our results are pertinent and may effectively contribute to the scientific debate on this issue.

The selection of patients at risk for hypotension may be seen as a limitation, as well; however, this was done in order to focus the study on patients who would truly benefit from the proposed strategies. Accordingly, the reported high incidence of nausea and/or vomiting has not to be seen as surprising, since enrolled patients were more likely to develop such symptoms.

Another limitation of the study may be due to the use of ephedrine. Historically, ephedrine was considered the vasopressor of choice in the management of maternal hypotension since its effects on placenta perfusion seemed to be minimal if compared to other vasopressors (29). However, recent studies suggest a possible superiority of phenylephrine over ephedrine in the

prevention of anaesthesia-induced hypotension during Caesarean delivery (20), although it seems that there are no differences between the two medications in the rescue treatment of hypotensive episodes (23, 24).

With regards to the infusion of ephedrine, the given dose of our study (0.625 mg/min) was low when compared to other studies evaluating the administration of 1 mg/min to 5 mg/min (21, 22, 30). However, ephedrine infusion was not constant in those studies, but rather titrated to SBP values. Cooper et al. initial infusion rate was 1mg/min, but then adjusted between 0.065 mg/min and 2 mg/min to maintain SBP at baseline(22); Mercier et al. infused ephedrine at an initial rate of 2 mg/min, then modified using a predefined algorithm to maintain SBP within 90% and 105% of baseline (21); Kang et al. started an infusion of 5mg/min ephedrine for 2 min, and then adjusted it to keep 90% to 100% baseline SBP (30). Therefore, no definitive assumptions can be made on the actual concentration of ephedrine infused in cited studies.

In conclusion, both studied strategies were safe and effective in facing maternal hypotension following spinal anaesthesia for Caesarean delivery. Our study results showed that the use of vasopressors was not disadvantageous; however, it did not even produce benefits compared to a non-pharmacologic strategy.

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Correspondance:
Michele Zasa, MD
University of Parma - Department of Anaesthesiology
Critical Care and Pain Medicine
Azienda Ospedaliero-Universitaria
via Gramsci 14, 43100 Parma (Italy)
Tel. +390521703567
Fax +390521702863
E-mail: michele.zasa@gmail.com