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Prenatal Methadone Exposure, Meconium Biomarker Concentrations and Neonatal Abstinence Syndrome

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Abstract

Aims—Methadone is standard pharmacotherapy for opioid-dependent pregnant women, yet the relationship between maternal methadone dose and neonatal abstinence syndrome (NAS) severity is still unclear. This research evaluated whether quantification of fetal methadone and drug exposure via meconium would reflect maternal dose and predict neonatal outcomes.

Design—Prospective clinical study

Setting—An urban drug treatment facility treating pregnant and post-partum women and their children

Participants—Forty-nine opioid-dependent pregnant women received 30–110 mg methadone daily.

Measurements—Maternal methadone dose, infant birth parameters and NAS assessments were extracted from medical records. Thrice-weekly urine specimens were screened for opioids and cocaine. Newborn meconium specimens were quantified for methadone, opioid, cocaine and tobacco biomarkers.

Findings—There was no relationship between meconium methadone concentrations, presence of opioids, cocaine and/or tobacco in meconium, maternal methadone dose or NAS severity. Opioid, cocaine and tobacco biomarkers also were found in 36.7, 38.7 and 81.1% of meconium specimens, respectively, and were associated with positive urine specimens in the third trimester. The presence of opioids other than methadone in meconium correlated with increased rates of preterm birth, longer infant hospital stays and decreased maternal time in drug treatment.

Conclusions—Methadone and its metabolite 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP) concentrations in meconium did not predict infant birth parameters or NAS severity.

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Prospective urine testing defined meconium drug detection windows for opiates and cocaine as three months, rather than the currently accepted six months. The presence of opioids in meconium could be used as a biomarker for infants at elevated risk in the newborn period.

INTRODUCTION

Methadone is standard pharmacotherapy for opioid-dependent pregnant women, and when combined with comprehensive prenatal care, is associated with improved obstetric and neonatal outcomes compared to non-treatment [1–6]. Most methadone-exposed infants develop neonatal abstinence syndrome (NAS), a constellation of symptoms of nervous, gastrointestinal and respiratory system dysfunction [7]. The dose-response relationship between maternal methadone pharmacotherapy and neonatal withdrawal has been extensively studied [8–17], but remains unclear. Similarly, methadone biomarker concentrations in maternal and neonatal specimens were examined as predictors of neonatal birth parameters, including gestational age, weight, length, among others [14,18–25], but data are inconsistent. Maternal plasma, serum, and urine methadone concentrations are considered indicators of recent exposure, while cumulative fetal exposure might better predict neonatal outcomes and be a more useful tool to identify substance-exposed, at-risk infants. Meconium, the first neonatal feces, starts forming in weeks 12–16 of gestation, and offers advantages over maternal urine testing at delivery due to longer drug detection windows, higher analyte concentrations and easier collection [26].

Controlled drug administration studies in pregnant women are rare because of obvious ethical concerns. Methadone pharmacotherapy during pregnancy offers a unique opportunity to examine maternal dose, biological specimen concentrations and neonatal outcome in an understudied and vulnerable population. Currently, meconium is thought to reflect second and third trimester drug exposure [27], but we [28] and others [29] suggest a shorter detection window of approximately three months for opioids and cocaine. Determining the drug detection window in meconium is critical to interpreting meconium toxicology results; if suspected drug exposure occurred early in pregnancy, an alternative matrix, i.e. maternal hair, would be necessary for objective documentation.

The primary aim of this research was to examine associations between methadone dose and meconium methadone and metabolite concentrations and determine whether meconium concentrations could predict the severity of NAS expression or infant birth parameters. A secondary aim was to determine if the presence of other opioids and/or cocaine, indicating maternal use of these drugs during gestation, was associated with poorer neonatal outcome. Additionally, the window of drug detection in meconium is objectively characterized using prospective maternal urine toxicology screens to monitor maternal use of substances during gestation. The present data will be beneficial to health care providers treating opioid-dependent pregnant women and/or their infants, clinical toxicologists interpreting meconium results, and those attempting to develop evidence-based drug policies.

METHODS

Forty-nine opioid-dependent and methadone-maintained pregnant women participating in three clinical protocols at the Center for Addiction and Pregnancy (CAP), Johns Hopkins Bayview Medical Center (JHBMC) were included in this report. CAP is an urban, multidisciplinary care treatment facility for pregnant drug-dependent women and their children, offering substance abuse treatment/mental health, obstetric and pediatric services [30–31]. Women provided written informed consent for participation in one of three Johns Hopkins University School of Medicine, JHBMC and/or National Institute on Drug Abuse (NIDA) Institutional Review Board-approved protocols evaluating voucher incentive

programs [32], comparing methadone and buprenorphine pharmacotherapy during pregnancy [33], or determining the concentrations of methadone in human milk and plasma and relationship to NAS expression and neonatal neurobehaviors [34]; the three studies had little temporal overlap, but in the event a woman met eligibility criteria for two or more studies, she was offered her choice of studies. For each protocol, participants were administered methadone under direct observation once daily unless split dosing was required. Total methadone dose was summed from conception (if the mother started methadone treatment prior to conception) or from methadone initiation (if the mother started methadone treatment after conception) until delivery, and third trimester dose was summed from 27 weeks and 0 day gestation (as determined by second trimester ultrasound) until birth; one participant's data were unavailable.

Research staff collected thrice-weekly observed urine specimens, with the number of specimens ranging from 7–74 (mean $\pm$ SD 32.4 ± 17.0) per participant, depending on enrollment length and clinic attendance. Abuscreen On-Trak Rapid Assays for Drug Abuse (Roche Diagnostic Systems,® Indianapolis, IN) were utilized for on-site opioid and cocaine screening tests, with positive results confirmed by gas chromatography mass spectrometry. At delivery, maternal and neonatal urine specimens were analyzed with BioRad Liquichek Immunoassay (BioRad Laboratories®, Hercules, CA) for cannabinoids, barbiturates, benzodiazepines, cocaine and opioids.

Maternal demographic information was obtained from CAP records. Infant data, extracted from medical records, included estimated gestational age at delivery, birth weight, length, head circumference, 1 and 5 min Apgar scores, and length of hospital stay.

Following birth, infants were assessed for NAS every 3–4 h for their entire hospital stay using a modified symptom-based version of the Finnegan Neonatal Abstinence Scoring System [7], with a maximum score of 42. Infants scoring ≥ 9 on two consecutive observations received pharmacological intervention. NAS peak score was the highest score on any NAS assessment. Hospital discharge for infants requiring pharmacological treatment of NAS occurred 24 h after weaning off medication. Infants not requiring pharmacotherapy for NAS were hospitalized for a minimum of 4 d after delivery.

Soiled diapers were collected from birth until the appearance of milk stool and the contents combined; thus, each baby had a single pooled meconium sample for analysis. All meconium samples were analyzed for methadone, EDDP, morphine, codeine, hydromorphone, hydrocodone, oxycodone, cocaine, benzoylecgonine, m-hydroxybenzoylecgonine and cocaethylene at NIDA [35–36] and/or the United States Drug Testing Laboratories (Des Plaines, IL); 37 specimens with sufficient meconium amount also were analyzed for amphetamine, methamphetamine, *p*-hydroxymethamphetamine, nicotine, cotinine and *trans*-3'-hydroxycotinine [36]. Total methadone concentrations were calculated as methadone plus EDDP molar equivalents.

Pearson correlations were calculated for normally distributed variables, as verified by the Kolmogorov-Smirnov Test. Non-parametric Spearman correlation coefficients, based on rank, were employed for non-normal distribution, including gestational age, 1 and 5 min Apgar scores, length of neonatal hospital stay, day of peak NAS score and meconium methadone concentrations. When comparing two data sets, χ^2 , t-tests or Mann-Whitney tests were employed as appropriate. P-values <0.05 were considered significant.

RESULTS

Maternal Characteristics and Methadone Dosing

Forty-nine opioid-dependent pregnant women, mean $\pm$ SD age 29.2 ± 4.9 years (range 19–39 years), participated. African-Americans comprised 57.1% of the population; 38.8% were Caucasian, and 2.0% identified themselves as other; 83.7% self-reported tobacco use. Methadone treatment was initiated prior to conception for 8.3% or in the first, second and third trimester for 25.0%, 54.2%, and 12.5%, respectively; the mean $\pm$ SD length of methadone maintenance during pregnancy was 21.8 ± 8.2 weeks (range 7.6–38.9 weeks). Dose at delivery ranged from 30–110 mg/d; most (81.6%) received between 50 and 100 mg/d. Fewer women received <50 mg/d (6.1%) or ≥ 100 mg/d (12.2%). Median (interquartile range) cumulative dose during enrollment and third trimester were 10,188 (6554–13,178) mg and 6163 (4790–7224) mg, respectively.

Urine Toxicology

Opioid use, other than methadone, during gestation was documented by urine toxicology in 64.6% of participants; for 43 women with complete urine data, the percentage of opioid-positive urine specimens ranged from 0 to 73.0% (mean $\pm$ SD $11.4 \pm 16.7\%$). Additionally, cocaine use was detected in 47.9% of all participants; for 43 women with complete urine data, the percentage of cocaine-positive urine specimens ranged from 0 to 63.3% ($7.3 \pm 12.2\%$). Illicit opiate and cocaine use appeared to decrease later in pregnancy as the frequency of positive urine specimens decreased in 67.6% and 55.4% of second-trimester opiate and cocaine users, respectively. At delivery, two women and their infants had opioid-positive urine tests; another mother/infant pair was positive for cocaine and opioids.

Neonatal Characteristics

Neonatal data are presented in Table 1. All were singleton births and appropriate in size for gestational age. Seventeen (34.7%) required pharmacotherapeutic intervention for NAS. Preterm birth (<37 weeks gestation) occurred in 18.4%. Mean peak NAS score was 9.7 ± 4.5 (range 3–26) observed 1 to 9 d post-delivery (median 3 d).

Meconium Methadone Results and Maternal Dose

All but one meconium specimen was positive for methadone and its primary metabolite, EDDP (Table 2). Methadone dose at delivery and cumulative doses throughout pregnancy and third trimester were not significantly correlated to meconium concentrations. Furthermore, methadone meconium concentrations were not correlated to infant birth parameters or the need for pharmacologic intervention for NAS.

Meconium Opioid and Cocaine Results and Maternal Urine Testing

There was evidence of maternal opioid use (other than methadone) in 36.7% of meconium specimens. Morphine was the most prevalent analyte (Table 2), but the heroin biomarker 6-acetylmorphine was not detected. Opioid presence in meconium was generally associated with a higher percentage of opioid-positive maternal urine specimens in the third trimester and/or continued use within two months of delivery (Figure 1), but there were exceptions. Morphine-positive meconium was noted in three infants whose mothers had no opiate-positive urine specimens, and in two cases where the last positive urine opioid tests were 75 and 128 d before delivery. Of three infants with opioid-positive urine at birth, only one had opioid-positive meconium.

Cocaine exposure was documented in 19 (38.8%) meconium specimens, most commonly by the presence of *m*-hydroxybenzoylecgonine (Table 2). Similar to opioids, cocaine-positive

meconium results were associated with higher third trimester cocaine-positive urine specimens and exposure continuing within three months of delivery (Figure 2). There were a few exceptions; two participants had cocaine-positive urine specimens 86 and 176 d before delivery and three never had positive urine specimens, yet meconium contained cocaine biomarkers. The one infant with cocaine-positive urine at birth also had cocaine-positive meconium.

Tobacco use was prevalent in this population by both maternal self-report and meconium testing. Forty-one (83.6%) women self-reported smoking cigarettes during pregnancy; of these, 29 meconium specimens were positive for at least one tobacco biomarker, two were negative and 10 could not be tested because of insufficient meconium. Among eight declared non-smokers, five meconium specimens were negative for nicotine and metabolites, one was positive, and two could not be analyzed.

Meconium Results as a Predictor of Neonatal Outcomes

Opioid- but not cocaine-positive meconium results were statistically more likely in premature infants (Table 3), but neither predicted the need for NAS pharmacotherapy. Daily methadone dose at delivery was not related to meconium results, but cumulative third trimester methadone dose was lower among those with opioid- or cocaine-positive meconium; however, these women also were methadone-maintained for less time. In addition, those with opioid-positive meconium remained in the hospital for longer and had a slightly delayed time to peak NAS score.

No significant differences in birth parameters or NAS severity were observed in infants with tobacco-positive or -negative meconium. All infants born prematurely had tobacco-positive meconium, but high rates of tobacco-positive results also were observed in term births (77.4%).

Maternal Dose as a Predictor of Neonatal Outcomes

Daily methadone dose at delivery, cumulative methadone dose during enrollment and total methadone dose during the third trimester were not associated with birth weight, length, head circumference, peak NAS score, day of peak NAS score, or need for NAS pharmacotherapy. Cumulative third trimester dose was positively correlated with gestational age at delivery ($r=0.469$, $p=0.001$), but dose at delivery was not. Also, cumulative third trimester dose was negatively related to neonates' length of hospital stay ($r=-0.403$, $p=0.005$) (Figure 3).

DISCUSSION

Methadone pharmacotherapy is the current standard of care for opioid-dependent pregnant women, yet despite over four decades of research, clinically relevant questions regarding the effects of methadone on neonatal outcomes remain. We evaluated whether quantification of methadone and other opioids, cocaine and nicotine in meconium reflects maternal methadone dose and is related to neonatal outcomes, including NAS.

Contrary to a report by Stolk et al. [37], meconium methadone and EDDP concentrations were associated neither with maternal daily methadone dose at delivery, nor with total or third trimester cumulative doses. The lack of a maternal dose-meconium concentration relationship is not surprising given that methadone dose is not correlated to plasma levels in pregnant women [34]. Furthermore, absorption, metabolism and excretion vary between individuals and are altered during pregnancy. Several studies demonstrated more rapid methadone elimination as pregnancy progresses [38–41], possibly due to cytochrome P450 enzyme induction [42]. Additionally, the placenta plays a role in fetal methadone exposure

[43]; transplacental permeability to methadone increases with gestational age, thought to be directly mediated by decreasing placental p-glycoprotein expression later in pregnancy [44]. Thus, maternal dose and hepatic function, placental maturity, gestational age, fetal liver development and excretion all influence fetal methadone exposure and subsequent disposition in meconium, perhaps contributing to the lack of a direct dose-concentration relationship.

Meconium methadone and EDDP concentrations were investigated as predictors of infant birth parameters and NAS severity; however, no significant relationships were observed. As methadone concentrations were not related to maternal dose or neonatal outcomes, meconium analysis could be limited to qualitative determinations of methadone biomarker presence or absence.

In one specimen, no methadone or EDDP was detected, although the mother received 110 mg daily at delivery, 10,580 mg during study enrollment, and 8700 mg in the third trimester. There is no clear explanation of why this meconium was negative for methadone biomarkers. It is highly unlikely that the woman did not take her prescribed daily dose, as daily methadone administration was directly observed at CAP to discourage drug diversion. Separate aliquots of the meconium specimen were analyzed, and both were negative, excluding potential analytical error. Analyte concentrations are known to change with successive bowel movements [45–46], and to fall below detectable limits a few days after birth. The time between birth and meconium collection was not recorded in this study, thus it is possible that several days had passed between birth and specimen collection. Misidentification of the specimen was unlikely, but cannot be ruled out.

An important strength of this research was thrice-weekly urine tests for illicit opiate and cocaine exposure during pregnancy, enabling an objective determination of meconium's drug detection window; few manuscripts to our knowledge describe urine toxicology results collected during pregnancy. In the present study, we observed some women with high percentages of positive urine tests (up to 73.0% for opiates and 63.3% for cocaine), but also some women with no positive tests; as a result, mean $\pm$ SD % positive urine specimens were $11.4 \pm 16.7\%$ for opioids and $7.3 \pm 12.2\%$ for cocaine. In a study by Fischer et al [13], methadone-maintained women had, on average, 4 opioid-positive urine specimens during treatment (collected twice weekly from enrollment at gestational weeks 24–29 until delivery); however, it is not clear what the variability was between subjects or what the percentage of positive specimens were. In another study conducted by CAP involving buprenorphine-maintained pregnant women, the percentage of positive urine tests collected throughout pregnancy was as high as 75.0% for opiates [28].

Most women had at least one opioid- and/or cocaine-positive urine specimen during gestation, and meconium analysis identified substantial opioid, cocaine and tobacco use. Meconium drug detection windows are thought to begin with meconium formation at about 12–16 weeks gestation, and extend until birth. Our data suggest that the detection window is shorter, with meconium reliably detecting drug use only within the last trimester. In addition to timing, frequency of drug use also was an important factor. For opiates and cocaine, high percentages of positive maternal urine specimens, particularly in the third trimester, were associated with positive neonatal meconium [28]. Yet in three cases each for opiates and cocaine, meconium specimens were positive without any documented gestational drug use. It is possible that in these cases, maternal urine contained drug, but at concentrations below the testing cutoff or women did not provide urine specimens shortly after drug use. Also, drug exposure identification prior to study entry in the second or sometimes early third trimester was by self-report only. Finally, urine specimens were unavailable when women

did not attend treatment daily, although urine tends to remain positive for several days after last use.

We did identify significant differences between children with opioid-positive and opioid-negative meconium, including a nearly two-fold increase in the length of hospitalization and lower cumulative maternal methadone doses, but no difference in need for NAS pharmacotherapeutic intervention. From our data, we cannot definitively attribute these outcomes as a consequence of maternal opioid use. Many of the children with opioid-positive meconium results also were premature, a factor associated with longer hospital stays [47]. Prematurity and the shorter duration of study enrollment would reduce the cumulative amount of methadone received; notably, mean dose at delivery was not significantly different for meconium opioid-positive or – negative results. Prematurity may also be influencing the NAS data, as NAS in premature infants is characterized by lower NAS scores, less need for medication and shorter hospitalizations for NAS-related problems [48]. Yet, premature infants are more likely to have other medical problems which cause them to have longer lengths of hospital stay.

No differences were observed for tobacco-exposed and unexposed infants, although only six infants had tobacco-negative meconium. Previous research documented a more severe [49] and extended NAS [16] in heavy smokers. We did not observe any trend between NAS maximum score and meconium nicotine biomarker concentrations. As we demonstrated for methadone, it is possible that a clear dose-concentration relationship does not exist for tobacco, which would explain why no correlation between meconium nicotine concentrations and neonatal NAS severity was found. Also, it is possible that neonatal nicotine withdrawal differs qualitatively and/or quantitatively from opioid withdrawal, or that tobacco users in this cohort were moderate to light smokers.

We did not observe significant relationships between maternal methadone dose and infant birth parameters including birth weight, length, head circumference or NAS severity. In this study, a modified Finnegan scale [7] was used to score NAS manifestation. As with all assessments of NAS, some inter-observer variability is expected, but we sought to minimize subjectivity between evaluators by clearly defining scoring criteria and providing extensive training to our nursing staff. Cumulative maternal methadone dose in the third trimester was correlated with older gestational age at delivery and decreased length of hospital stay for infants. Our data support the Center for Substance Abuse Treatment recommendation that dosing decisions should be based on maternal drug craving and relapse potential [50]. However, women in our study received methadone doses ≤ 110 mg/d at delivery; effects of higher methadone doses cannot be extrapolated from our data. Recently, high doses of methadone (>140 mg/d) were associated with an increased need for NAS treatment and longer NAS duration [9].

In conclusion, meconium testing is a sensitive measure of prenatal methadone, opioid and cocaine exposure during the third trimester, not the second and third trimester as currently assumed. The presence of non-methadone opioids in meconium was associated with poorer neonatal outcomes, such as longer hospital stay, and may be a useful biomarker of poorer neonatal outcomes.

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Figure 2.
Percentage of cocaine-positive urine specimens collected in second (□) and third trimester (■) and days between the last known cocaine-positive urine specimen and delivery (●) among mothers of infants with negative (N=28) or positive (N=15) meconium specimens

Figure 3.
Significant correlations between cumulative third trimester methadone dose and gestational age and neonatal length of stay

Table 1

Birth outcomes of 49 infants prenatally exposed to methadone

	N	%	Mean	SD	Median	Range
Gestational age (weeks) [/]					39.3	30.4 – 42.0
≥37 weeks	40	81.6				
35–37 weeks	4	8.2				
32–35 weeks	4	8.2				
<32 weeks	1	2.0				
Birth weight (g)			3032	613	2940	1505 – 4810
Head circumference (cm)			32.9	1.8	33	26 – 36
Length (cm)			49.1	3.4	49	41 – 56
Apgar score – 1 min [/]					8	5 – 8
Apgar score – 5 min [/]					9	8 – 9

[/] Data do not follow a normal distribution; therefore, mean and standard deviation data are not included

Table 2

Methadone, opioids, cocaine, tobacco and amphetamines biomarkers in meconium of 49 infants prenatally exposed to methadone

	N positive	Median (ng/g)	Range (ng/g)
<i>Methadone</i>			
Methadone	48	5,234	85 – 21,980
EDDP	48	33,193	4431 – 101,021
<i>Opioids</i>			
6-Acetylmorphine ^I	0		
Morphine	17	65.9	7.5 – 3,622
Codeine	2	141.0	16.3 – 266
Hydromorphone	1	21.0	
Hydrocodone	0		
Oxycodone	0		
<i>Cocaine</i>			
Cocaine	3	13.0	4.4 – 233
Benzoylcegonine	6	28.5	2.4 – 969
<i>m</i> -Hydroxybenzoylcegonine	18	62.7	8.4 – 254
Cocaethylene	0		
<i>Tobacco</i>			
Nicotine ^I	29	59.4	2.6 – 383
Cotinine ^I	30	89.2	22.7 – 915
<i>trans</i> -3'-Hydroxycotinine ^I	30	276	57 – 4,259
<i>Amphetamines</i>			
Methamphetamine ^I	0		
Amphetamine ^I	0		
<i>p</i> -Hydroxymethamphetamine ^I	0		

^I Analyzed in 37 specimens with sufficient meconium

Table 3

Neonatal outcomes and maternal dosing among 49 infants with meconium opiate- and cocaine-positive tests

	Opioid ¹ -Positive Meconium (N=18)	Opioid ¹ -Negative Meconium (N=31)	p-value
Neonatal Outcome			
Gestational Age (weeks) ²	38.0	40.0	0.007*
Premature (%)	38.9	6.5	0.005*
Birthweight (g)	2823 ± 554	3154 ± 621	0.068
Length (cm)	48.0 ± 3.6	49.7 ± 3.1	0.085
Head circumference (cm)	32.5 ± 1.6	33.1 ± 1.9	0.306
Length of hospital stay (d) ²	8.5	4.5	0.018*
Peak NAS score	10.2 ± 5.7	9.4 ± 3.6	0.526
Day of peak NAS score ²	3.5	3.0	0.035*
Require NAS Pharmacotherapy (%)	33.3	35.5	0.879
Maternal Methadone Treatment			
Weeks in Treatment	18.0 ± 8.5	24.1 ± 7.1	0.009*
Dose at Delivery (mg/d)	76.1 ± 17.5	76.9 ± 18.5	0.879
Cumulative dose during enrollment (mg)	7734 ± 4472	12009 ± 5086	0.005*
Cumulative dose in third trimester (mg)	5049 ± 1603	6464 ± 1670	0.008*
	Cocaine-Positive Meconium (N=19)	Cocaine-Negative Meconium (N=30)	p-value
Neonatal Outcome			
Gestational Age (weeks) ²	38.3	39.8	0.128
Premature (%)	31.6	10.0	0.057
Birthweight (g)	2940 ± 660	3090 ± 586	0.412
Length (cm)	48.2 ± 3.3	49.7 ± 3.4	0.162
Head circumference (cm)	32.8 ± 1.4	32.9 ± 2.0	0.914
Length of hospital stay (d) ²	7.0	5.0	0.869
Peak NAS score	10.0 ± 4.3	9.5 ± 4.6	0.699
Day of peak NAS score ²	3.0	3.0	0.314
Require NAS Pharmacotherapy (%)	36.8	33.3	0.801
Maternal Methadone Treatment			
Weeks in Treatment	17.5 ± 6.4	24.6 ± 8.0	0.002*
Dose at Delivery (mg/d)	72.6 ± 16.5	79.2 ± 18.6	0.218
Cumulative dose during enrollment (mg)	7430 ± 3370	12355 ± 5388	0.001*
Cumulative dose in third trimester (mg)	5388 ± 1783	6290 ± 1797	0.095

¹Excluding methadone²Data do not follow a normal distribution; therefore, median data are provided

*P<0.05