Chapter 10

Comparison of induction of labor and expectant monitoring in intrauterine growth restriction at term through integration of trial outcomes and patient preferences

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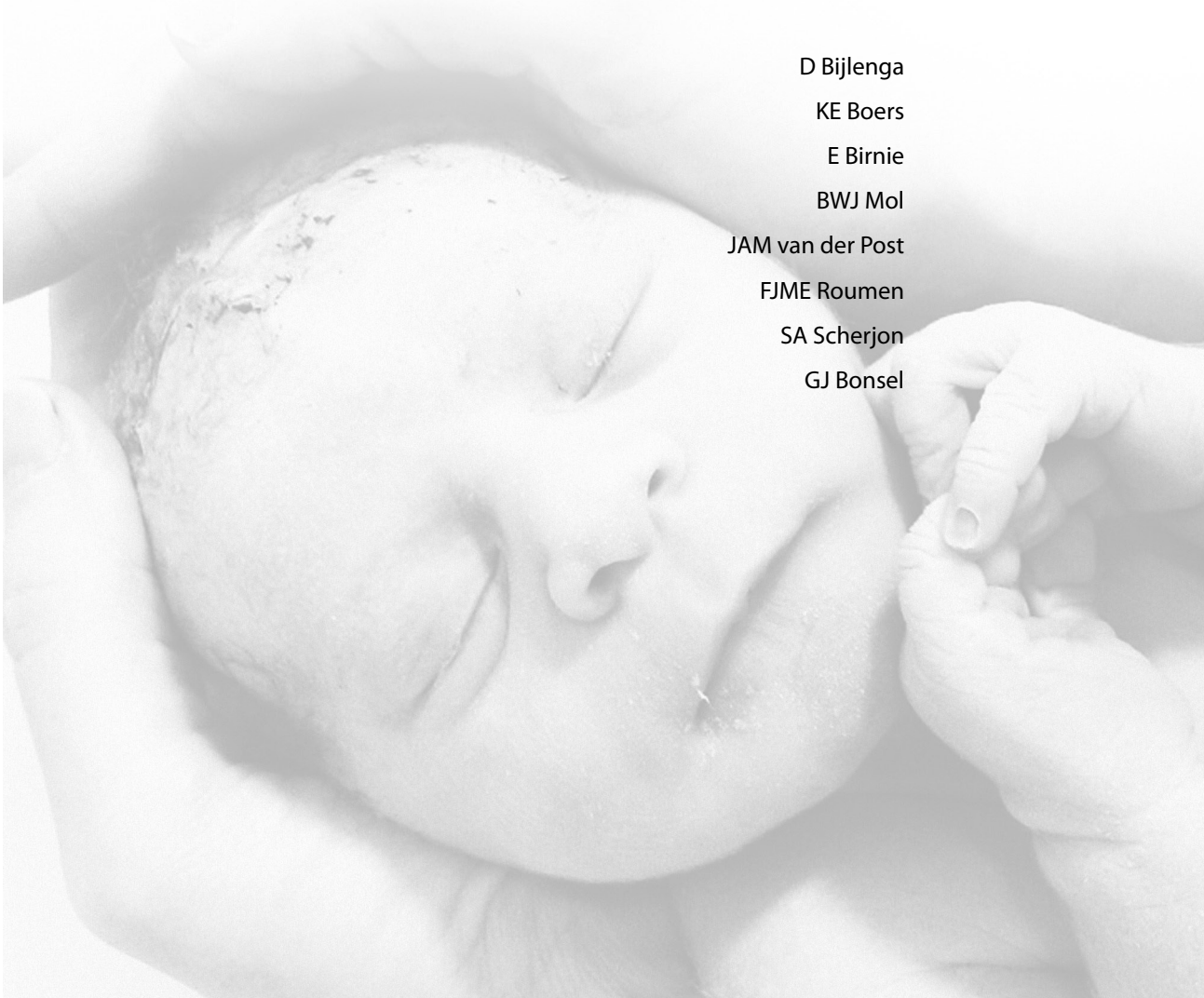

Abstract

Objective: Intrauterine growth restriction (IUGR) is associated with an increased risk for neonatal morbidity and mortality. When diagnosed at or near term, a possible treatment for IUGR is induction of labor. In DIGITAT, a large Dutch multicentre randomized controlled trial (RCT), we found no differences in neonatal outcome or mode of delivery between induction of labor and expectant management. The aim of this patient's preference study alongside the RCT was to gain insight into how women value different obstetrical outcome scenarios. These values, in combination with the outcome distribution of the RCT, will indicate the preferred treatment in women with suspected IUGR after 36 weeks of pregnancy.

Methods: In the DIGITAT trial, 626 women with IUGR at term were randomized for induction of labor or expectant management. We used case scenarios ('vignettes'), involving five important factors ('attributes') that were evaluated by 24 trial participants using a discrete choice experiment (DCE) and by visual analogue scale (VAS). We combined these outcome valuations with outcome distributions of the RCT, and calculated a mean outcome for the strategies induction of labor and expectant management, respectively. These mean values were compared between the treatment groups using t-test for the total group and for subgroups, which were defined according to parity and gestational age.

Results: Using the DCE there was no overall treatment preference for the total group or for any of the subgroups ($p=.72$). The VAS, however, did indicate preference towards expectant management for the total group ($p<.001$) as well as for subgroups.

Conclusion: Based on the theoretical superiority of the DCE over the VAS method, the DCE results are leading. Patient's preferences for expectant monitoring and induction of labor in case of IUGR at term are equal. These results reflect the outcomes of the DIGITAT trial.

Introduction

Evaluation of medical interventions in clinical problems is often difficult because various outcomes are involved. In obstetrics, not only survival, but also the long-term health of mother and child, as well as complications with short-term consequences and the mode of delivery all should be considered in the decision which intervention is the best. An example of an obstetric problem where various outcomes need to be considered is intrauterine growth restriction (IUGR) at term. In pregnancies complicated by IUGR at term there is an increased risk for neonatal morbidity and perinatal mortality, and there is concern about the long term health of the child [1-5]. In case of IUGR at term, there are two treatment options: The pregnancy can be monitored expectantly, or labor can be induced. Induction of labor might prevent neonatal morbidity and perinatal mortality and it may improve long-term outcomes, but it also interferes with the process of natural birth at a possible increased risk of instrumental delivery.

In the Disproportionate Intrauterine Growth Intervention Trial At Term (DIGITAT; ISRCTN10363217), a large nationwide multicentre randomized controlled trial (RCT), induction of labor was compared to expectant monitoring in women with an IUGR-fetus beyond the 36th week of pregnancy. The study showed that in both strategies neonatal morbidity, the number of instrumental deliveries, and maternal outcomes were not different. There were also no differences in overall maternal health-related quality of life (HR-QoL) [6-8]. It was concluded that both strategies appear equivalent in terms of neonatal and maternal health. However, in the accompanying editorial it was stated that, as the association between suboptimal growth and stillbirth is well accepted, it is appropriate to counsel the women because in a suspected growth-restricted pregnancy beyond 36 weeks, induction of labor may prevent the rare but devastating outcome of stillbirth. Whereas this strategy does not increase maternal risk, it might be the preferred option for many women [9].

Alongside DIGITAT we performed a patients' preference study, in which patients

gave their valuations of different health outcome scenarios that were measured in DIGITAT. By combining true DIGITAT outcome data with the patients' valuations of those outcomes, the result is an overall valuation of the outcomes in terms of preference from patients' point of view. Regarding the equivalency of the DIGITAT outcomes, patients' preference can be put forward as the most important indicator for the evaluation of all outcomes taken together in the ultimate choice of treatment [10].

In this paper we present the expected patients' preference of treatment in case of IUGR at term. The treatment options are induction of labor or expectant monitoring. We combined the DIGITAT outcomes with patients' valuations of those outcomes. We evaluated preferences for the total group, as well as for subgroups based on gestational age and obstetric history.

Methods

General approach

The clinical data originated from DIGITAT (Disproportionate Intrauterine Growth Intervention Trial At Term ISRCTN10363217 [6], a multicentre randomized controlled trial (RCT) performed in the Netherlands between November 2004 and November 2008. The 650 included patients with a singleton pregnancy beyond 36+0 weeks gestation with suspected IUGR were randomly allocated to either induction of labor within 48 hours or to expectant management. Main outcome measure was a composite of adverse neonatal outcome, defined as neonatal death before hospital discharge, a 5-minute Apgar score < 7, an umbilical artery pH <7·05 or admission to the neonatal intensive care unit. More details are provided in the original paper [8].
To arrive at the comparison of the patients' preference between induction of labor and expectant management in case of IUGR at term, we made three steps. First, we developed and tested case scenarios among women who had participated in the DIGITAT study and women who were asked but had refused. Second, we combined

the obtained patients' valuations' with the observed clinical outcome data of the DIGITAT study, as well as rates obtained from the literature. From this combined dataset we calculated sum-scores for patients' preferences per treatment allocation (induction or expectant management), and tested for differences between the treatments. Below we discuss these three steps.

Step 1: Development of case scenarios ('vignettes')

In the development of case scenarios, we first aimed to identify the most important factors that were involved in the choice between induction of labor and expectant monitoring. To do so, we conducted interviews about the physical, psychological, and social burden and consequences of IUGR in a previous study [11]. The interviewees were 10 women who participated in DIGITAT or HYPITAT (Hypertension and Preeclampsia Intervention Trial at Term [12] studies, and 10 medical experts (gynecologists, obstetricians, neonatologists, pediatricians). The interviews led to the definition of potential attributes: 'Maternal health ante partum', 'time between diagnosis and delivery', 'process of delivery', 'maternal outcome', and 'neonatal outcome'. Each attribute incorporated several levels. For example, in case of the attribute process of delivery, we considered the attributes spontaneous onset of labor versus induction and primary caesarean section, as well as the mode delivery (vaginal, vacuum or caesarean section), in all possible combinations (Table 1). For each attribute, we defined two to seven levels according to the interviewees' responses, literature review, and expected primary and secondary outcomes from DIGITAT. More information about the vignettes is provided in a separate publication on this study (Bijlenga, Birnie, Bonsel, 2009 [11].

Step 2: Obtaining patient valuations of case scenarios

Patients' valuations of the vignettes were established in group sessions [13]. Participants were 24 patients (other than the pilot participants) who participated to either DIGITAT or to a similar RCT about treatment preference in case of pregnancy-induced hypertension (the HYPITAT trial [12]. All participants valued the vignettes using the widely used weighting method discrete choice experiment (DCE) [13]. The

DCE is believed to be a valid method to calculate utility and preference [14;15]. We also show the results based on the visual analogue scale (VAS) values, which are not considered as a measure of preference, but may give support to the DCE outcomes [16;17]. The mean assigned weights using the methods in our previous study are shown in Table 1. Higher DCE and VAS valuation indicate higher preference. For example, the attribute 'Neonatal outcome' has lower preferences the worse the description of the levels. This indicates less preference of the higher levels of neonatal outcomes as compared to the baseline neonatal level 'No complications'.

The health-related quality of life (HR-QoL) outcomes of the DIGITAT patients were also used in this study [6;7]. As part of the HR-QoL, the participating women filled out the European Quality of life (EQ5D) at inclusion, 6 weeks postpartum, and 6 months postpartum. The EQ5D is a brief validated measure that provides a global health state rating of mobility, self-care, usual activities, pain/discomfort, and anxiety/depression [18]. Details of the DIGITAT HR-QoL study are described elsewhere [8]. Using the HR-QoL outcomes we calculated the weights for the attributes Maternal health ante partum and for Maternal outcome (post partum), see also Table 1.

Step 3: Combining patient valuations and outcome data of the DIGITAT trial

In order to combine the patient valuations of the vignettes and the outcome data of the DIGITAT trial, we needed to define which DIGITAT outcomes can be assigned to which level of the attributes. Therefore, we defined 'translation rules' (see Table 1). Most DIGITAT cases could be assigned using the translation rules, see Table 1. Some cases, however, were unclear to which of two adjacent levels they should be assigned. We presented these ambiguous cases to three neonatologists and asked them to which of the two adjacent levels they should be assigned.

Whereas we did not have any data on neonatal mortality from the DIGITAT trial, we used perinatal and neonatal mortality incidence data from the Dutch neonatal registry (PRN 2009) for the calculation of preference for the total group. These data are presented in Table 1 (attribute 5, level 5).

Table 1
Translation rules to assign every clinical case to a level per attribute using observed clinical data from DIGITAT, and its DCE value (significant values are signed by *).

Attribute	Used variable(s)	Level	Translation rules	DCE values patients	DCE values Lay people
A1: Maternal health ante partum	- RCT data: fetal movement, fetal cardiotocography (CTG).	L1	All of the following: EQ Mobility<3; EQ Pain/Discomfort<3; EQ Anxiety/Depression<3; normal fetal movement; good fetal CTG.	Ref	Ref
	- HR-QoL data at inclusion: EQ Mobility, Pain/Discomfort, Anxiety/Depression	L2	At least one of the following: EQ Mobility=3; EQ Pain/Discomfort=3; EQ Anxiety/Depression=3; decreased fetal movement; suboptimal fetal CTG.	0.3	-0.8
A2: Time between diagnosis and delivery	- RCT data: number of days between inclusion date and delivery date.	L1	≤ 3 days	Ref	Ref
		L2	> 3 days	5.3*	-0.6
A3: Process of delivery	- RCT data: induction of labor and mode of delivery.	L1	Vaginal delivery	Ref	Ref
		L2	Induction of labour and vaginal delivery	2.3	-6.2*
		L3	Vacuum or forceps	3.9	-1.4
		L4	Induction of labour and vacuum or forceps	11.3	-1.1
		L5	Primary caesarean	9.3	1.1
		L6	Secondary caesarean	9.3	2.6
		L7	Induction of labour and secondary caesarean	2.5	2.3
A4: Maternal outcome	- RCT data: maternal length of hospital stay, type of hospital stay. - HR-QoL data at 6 months post partum: EQ Mobility, Pain/Discomfort.	L1	All of the following: No stay; stay at the ward; ≤ 5 days stay at Medium care; EQ Mobility<3; EQ Pain/Discomfort<3.	Ref	Ref
		L2	At least one of the following: 6 to 10 days stay at Medium care; < 5 days stay at High or Intensive care with ≤ 10 days total stay; EQ Mobility<3; EQ Pain/Discomfort<3.	-7.2	-4.3*
		L3	At least one of the following: > 10 days stay at Medium care; ≥ 5 days stay at High or Intensive care; EQ Mobility=3; EQ Pain/Discomfort=3.	-12.6*	-16.3*
A5: Neonatal outcome	- RCT data: neonatal length of hospital stay, type of hospital stay, type of complications; diagnosis at discharge.	L1	No hospital stay or stay at maternal ward.	Ref	Ref
		L2	Stay at Medium care ≤ 10 days.	7.6*	-2.3
		L3	At least one of the following: > 10 days stay Medium care; ≤ 5 days at high or intensive care; total hospital stay ≤ 14 days; diagnosis at discharge is not chronic disease.	1.0	-6.8*
		L4	At least one of the following: > 5 days at High or Intensive care; diagnosis at discharge is chronic disease.	-9.3*	-20.8*
		L5	Perinatal or neonatal death.	-13.8*	-33.1*

We combined the clinical dataset and the patient's valuations, using the translation rules. For example, if treatment X resulted in 11% and treatment Y in 9% secondary caesarean sections, and the preference value for caesarean section is -0.2, then the summed score for caesarean section in treatment X is -0.2*0.11= -0.022 and for treatment Y is -0.2*0.09= -0.018. In this example treatment Y is the preferred option since its sum-score is higher. Using paired t-test (in case of normal distributions) we made straightforward comparisons of the summed score for preference for induction of labor versus expectant monitoring. We compared both the preference scores for the total group as well as for subgroups based on gestational age at inclusion (≤ 36+6, 37 to 38+6, and ≥ 39 weeks) and parity (nulliparous, multiparous). Analyses were conducted with SPSS 16.0 for Windows (SPSS Inc). A p-value ≤0.05 (two sided) was considered to indicate statistical significance.

Results

For this study we used data of all 650 randomized DIGITAT women, of which 321 women had been randomized for induction of labor and 329 for expectant management.

All maternal and procedural data could be directly translated to the attributes using the translation rules (Table 1). However, of the neonatal cases, 42 could not be straightforwardly translated to the either of the levels. A panel of three neonatologists assigned 11 of these neonatal cases to Attribute 5 (neonatal outcome), level 3 (A5L3) and 31 cases to A5L4 (Table 1). After the translation of all clinical outcomes into the appropriate attributes and levels, the outcome distributions for the total group and for the subgroups emerged (Table 2).

Table 2
Observed outcome distribution in percentages according to treatment (20), for each attribute-level separately, for all patients and for the subgroups of patients based on parity and gestational age at inclusion. For an explanation of the Attributes and levels, see table 1.

			Subgroups: parity				**Subgroups: gestational age at inclusion**					
Attribute (A) and Level (L)	Total group N=650		Nullipara n=383		Multipara n=266		G1 n=165		G2 n=383		G3 n=101	
	IL	EM	IL	EM	IL	EM	IL	EM	IL	EM	n=383	EM
A1L1	88.8	85.7	87.9	88.1	89.9	82.0	90.1	79.8	89.3	88.2	84.1	86.2
A1L2	11.2	14.3	12.1	11.9	10.1	18.0	9.9	20.2	10.7	11.8	15.9	13.8
A2L1	87.2	11.9	86.6	12.4	88.5	11.0	84.0	11.9	87.2	9.6	93.2	19.3
A2L2	12.8	88.1	13.4	87.6	11.5	89.0	16.0	88.1	12.8	90.4	6.8	80.7
A3L1	3.4	40.2	3.3	37.8	3.6	44.1	2.5	27.2	2.0	44.9	11.4	43.1
A3L2	74.1	37.8	61.3	31.3	90.6	48.0	75.0	42.2	76.0	38.0	63.6	31.0
A3L3	0.3	3.7	0.6	5.5	0	0.8	0	3.6	0.5	2.7	0	6.9
A3L4	8.1	4.6	14.4	7.0	0	0.8	6.3	4.8	7.1	4.3	15.9	5.2
A3L5	0.6	3.4	1.1	3.0	0	3.9	0	6.0	1.0	2.1	0	3.4
A3L6	0	2.1	0	3.0	0	0.8	0	1.2	0	1.6	0	5.2
A3L7	13.4	8.2	19.3	12.4	5.8	1.6	16.3	14.5	13.3	6.4	9.1	5.2
A4L1	97.4	99.1	95.4	99.0	100	99.2	98.7	97.6	97.3	9.4	95.3	100
A4L2	1.0	0.6	1.7	0.5	0	0.8	1.3	1.2	0.5	0.6	2.3	0
A4L3	1.6	0.3	2.9	0.5	0	0	0	1.2	2.1	0	2.3	0
A5L1	48.8	59.4	42.5	53.8	56.8	68.0	27.5	44.6	55.1	64.9	59.1	63.2
A5L2	32.2	21.5	35.9	24.9	27.3	16.4	40.0	21.7	29.6	22.2	29.5	19.3
A5L3	15.0	13.5	17.1	15.7	12.2	10.2	26.3	21.7	11.2	10.3	11.4	12.3
A5L4	4.1	5.5	4.4	5.6	3.6	5.5	6.3	12.0	4.1	2.7	0	5.3
A5L5	0.001*	0.005*	0	0	0	0	0	0	0	0	0	0

Note: IL= Induction of labor; EM= Expectant monitoring; G1= Gestational age ≤ 36+6 weeks at inclusion; G2= 37 to 38+6 weeks; G3= ≥ 39 weeks.
* Data from the Dutch neonatal registry (PRN 2009)

From the calculation of the valuation per attribute, we calculated the valuation distributions for the total group and for the subgroups using the patients' DCE and VAS valuations. All distributions were considered normal. The results of the t-test comparisons between the treatment options for the total group and for the subgroups are shown in Table 3. The table shows overall preference for expectant management in the total group as well as in the subgroups. The DCE preferences were equal between treatment options for both the total group and the subgroups. The VAS outcomes showed a treatment preference for expectant monitoring in the total group (p<.001) as well as for several subgroups (see Table 3).

Table 3
Comparison of the overall preference score according to treatment (20), for all patients and for the subgroup of patients, using the significant patient's and lay people's DCE values. Higher scores indicate stronger preference.

	DCE patient's valuations *			DCE lay people's valuations		
(Sub)groups	IL Mean (SD)	EM Mean (SD)	p	IL Mean (SD)	EM Mean (SD)	p
Total group (N=650)	-0.57 (2.39)	-0.51 (2.11)	.717			
Total group with PRN data	-0.59 (2.39)	-0.58 (2.11)	.945			
Subgroup Nullipara (n=383)	-0.79 (2.82)	-0.54 (2.17)	.326			
Subgroup Multipara (n=266)	-0.28 (1.60)	-0.46 (2.03)	.434			
Subgroup G1 (n=165)	-0.63 (2.35)	-1.05 (2.96)	.336			
Subgroup G2 (n=383)	-0.61 (2.50)	-0.26 (1.53)	.102			
Subgroup G3 (n=101)	-0.29 (1.92)	-0.54 (2.19)	.570			
Subgroup Nullipapa*G1 (n=95)	-0.89 (2.76)	-1.05 (2.97)	.780			
Subgroup Nullipara*G2 (n=204)	-0.86 (2.99)	-0.27 (1.58)	.082			
Subgroup Nullipara*G3 (n=65)	-0.34 (2.34)	-0.52 (2.16)	.884			
Subgroup Multipara*G1 (n=59)	-0.29 (1.64)	-1.03 (2.98)	.231			
Subgroup Multipara *G2 (n=164)	-0.32 (1.72)	-0.24 (1.48)	.733			
Subgroup Multipara *G3 (n=30)	0.00 (0.00)	-0.58 (2.32)	.359			

* The highly improbable significant weight for A5L2 has been ignored.
Note: G1= Gestational age ≤ 36+6 weeks at inclusion; G2= 37 to 38+6 weeks; G3= ≥ 39 weeks.

Discussion

We have taken all RCT data outcomes together and evaluated these in terms of patients' preference for induction of labor or expectant management in case of IUGR at term. We compared the summed valuations of the DIGITAT outcomes [8].

Our results show that, taken the outcomes of the total group, the DCE method did not indicate one preferred treatment over the other. The VAS indicated expectant management as an overall treatment preference. Also for most of the subgroups, which have been established according to the patient's parity and gestational age, the VAS indicated preference towards expectant management. These findings are supplemental to, and a reflection of, the outcomes of the clinical trial [8]. These results do not indicate either induction of labor or expectant management to be superior in terms of patient's preferences.

The DCE as a measure of preference is considered theoretically superior to the VAS. However, both the VAS and the DCE have their limitations. First of all, our main choice of method was the DCE method, which has proven to be a valid preference elicitation method in health care [19]. However, as our previous research has indicated, the outcome may depend on the choice of method [11]. We have backed up the DCE outcomes by VAS outcomes, which gave different results. According to the VAS outcomes, expectant management is superior in terms of patient's preferences. However, the DCE outcomes are here the leading outcomes, which do not reflect superiority of any treatment. Second, in this paper we solely discuss patient's preferences, while previous study shows that doctor's and the general public's preferences may differ[13]. We have limited our focus to patients, whereas in practice, patients are the key decision-makers in this particular setting. Finally, our study has focused on preference elicitation on the group level. Individual preferences may be different from the outcomes on the group level. We have observed in the DIGITAT trial that most patients did not want to participate as randomized patients indicated they wanted to wait instead of being randomized with a 50% chance of

induction of labor [8]. This prior preference for expectant management is reflected in the VAS results, but not in the DCE results. While this does not mean that the DCE is a less valid valuation method, it does seem to reflect revealed preferences less accurate than the VAS.

In short, the equivalence of the patient's preference scores for treatments in case of IUGR after 36 weeks of gestation reflects the equivalence of the clinical DIGITAT outcomes. Both treatments are safe and result in equal maternal and neonatal outcomes and preferences.

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